522 Rec'd PCT/PTO 16 JAN 2001 ORIGINAL

FORM PTO-1390 (REV 12-29-99) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: LEA 33 820

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): 09/743827

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB99/02267	14 July 1999 (14.07.99)	14 July 1998 (14.07.98)

TITLE OF INVENTION: ANTIPARASITIC ARTEMISININ DERIVATIVES (ENDOPEROXIDES)

APPLICANT(S) FOR DO/EO/US: HAYNES, Richard; CHAN, Ho-Wai; LAM, Wai-Lun; TSANG, Hing-Wo; CHEUNG, Man-Ki

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [ ] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information:

1) Certificate of Mailing under 37 C.F.R. 1.10;

2) Transmittal of Information Disclosure Statement under 37 C.F.R. 1.97(b);

3) Information Disclosure Citation (Modified Form PTO-1449) and references cited therein; and

4) Return Receipt Post Card.

Date of Deposit: 16 January 2001
Express Mail Label No. EK662543140US

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/743827	PCT/GB99/02267	LEA 33 820

17. [X] The following fees are submitted:	CALCULATIONS	PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$970.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$840.00**		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$690.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$670.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) **$96.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	27 - 20 =	7	X **$18.00**	$ 126.00	
Independent claims	11 - 3 =	8	X **$78.00**	$ 640.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$260.00**	$	
TOTAL OF ABOVE CALCULATIONS =				$ 1,626.00	
Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also by filed (Note 37 CFR 1.9, 1.27, 1.28).				$	
SUBTOTAL =				$ 1,626.00	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	
TOTAL NATIONAL FEE =				$ 1,626.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$	
TOTAL FEES ENCLOSED =				$ 1,626.00	
				Amount to be refunded:	$
				charged:	$

a. [ ] A check in the amount of $_____ to cover the above fees is enclosed.

b. [X] Please charge my Deposit Account No. 13-3372 in the amount of $ 1,626.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-3372. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Jeffrey M. Greenman
Vice President, Patents and Licensing
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516

Jerrie L. Chiu
SIGNATURE:

Jerrie L. Chiu
NAME

41,670
REGISTRATION NUMBER

Rec'd PCT/PTO 31 JUL 2001
09/743827

PATENT
Atty. Docket No.: Le A 33 820

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Cheung, *et al.*

SERIAL NO.: 09/743,827

FILING DATE: January 16, 2001

TITLE: Antiparasitic Artemisinin Derivatives (Endoperoxides)

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This Preliminary Amendment is submitted in the above-captioned application having U.S. Serial No. 09/743,827. Please amend the application as follows:

In the Claims

Please cancel claims 14, 15 and 24-27.

Please amend claims 1-13, 16, 17, 19, 20 and 22, as shown in the attached sheets. A marked version of the claim set showing the changes made is also attached.

Please add new claim 28, as shown in the attached sheet.

Remarks

By way of this Preliminary Amendment, claims 1-13, 16-23 and 28 are pending. Claims 14, 15 and 24-27 have been canceled, and claims 1-13, 16, 17, 19, 20 and 22 have been amended. New claim 28 has been added. These claim cancellations, amendments and additions are being made solely for purposes of placing the claims in a format appropriate for U.S. prosecution. No new matter was added by way of these claim amendments and additions.

More specifically, claims 1-13 are being amended to convert the Swiss-type use claim to the U.S. method of treatment format. Claim 16 is being amended to remove the improper multiple dependent claim format in compliance with 37 C.F.R. § 1.75(c) and to make it independent by adding material from claim 1. Claim 17 is being amended to separate the claim into two claims. Material deleted from claim 17 has been rewritten in dependent form in new claim 28. Finally, claims 19, 20 and 22 are being amended to specify that "Y" is as defined in claim 16 and to change claim dependencies. Applicants submit that all of these amendments do not change the scope of the claims as originally filed, because the amendments are being made solely to place the claims in a format appropriate for U.S. prosecution. Such amendments are therefore made to address formalities in the claim format and are not related to the patentability of the subject matter of the claims.

Conclusion

Applicants believe that the subject matter of the pending claims is patentable and that the instant application should accordingly be allowed. If the Examiner believes that a conversation with Applicants' attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned attorney at (203) 812-3964.

Respectfully submitted,

Dated: July 24, 2001

Jerrie L. Chiu
Attorney for Applicants
Reg. No. 41,670

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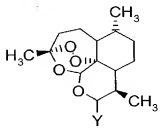
Amended Claims for U.S.S.N. 09/743,827 (Attorney Docket No. Le A 33 820)

1. (Amended) A method of treating or preventing a disease caused by infection with a parasite other than an organism of the genus Plasmodium, comprising administering to a host in need thereof an effective amount of a compound of the general formula I



(I)

or a salt thereof,

in which

Y represents a halogen atom, an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclylalkyl group or a group $-NR^1R^2$; where

R^1 represents a hydrogen atom or an optionally substituted alkyl, alkenyl or alkynyl group;

R^2 represents an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl group; or

R^1 and R^2 together with the interjacent nitrogen atom represent an optionally substituted heterocyclic group or an amino group derived from an optionally substituted amino acid ester.

2. (Amended) The method of claim 1, in which Y represents a halogen atom.

3. (Amended) The method of claim 2, in which Y represents a fluorine or bromine atom.

4. (Amended) The method of claim 1, in which Y represents a C_{3-8} cycloalkyl group, a C_{6-18} aryl group, a 5- to 10-membered C-linked heteroaryl group or a 5- to 10-membered heterocyclyl-C_{1-6} alkyl group, each group being optionally substituted by one or more substituents selected from the group consisting of halogen atoms, hydroxyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, carboxyl, C_{6-10} aryl, 5 to 10-membered heterocyclic and C_{1-4} alkyl- or phenyl-substituted 5- to 10-membered heterocyclic groups.

5. (Amended) The method of claim 4, in which Y represents a C_{6-18} aryl group optionally substituted by one or more substituents selected from the group consisting of halogen atoms, hydroxyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino and carboxyl groups.

6. (Amended) The method of claim 4, in which Y represents a phenyl, naphthyl, anthryl or phenanthryl group, each group being optionally substituted by one or more substituents selected from the group consisting of halogen atoms and hydroxyl, methyl, vinyl, C_{1-4} alkoxy and carboxyl groups.

7. (Amended) The method of claim 4, in which Y represents a phenyl, fluorophenyl chlorophenyl, bromophenyl, trimethylphenyl, vinylphenyl, methoxyphenyl, dimethoxyphenyl, trimethoxyphenyl, carboxylphenyl, naphthyl, hydroxynaphthyl, methoxynaphthyl, anthryl or phenanthryl group.

8. (Amended) The method of claim 7, in which Y represents a phenyl or trimethoxyphenyl group.

9. (Amended) The method of claim 1, in which Y represents a group $-NR^1R^2$ where R^1 represents a hydrogen atom or a C_{1-6} alkyl group and R^2 represents a C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{6-10} aryl or C_{7-16} aralkyl group, or R^1 and R^2 together with the interjacent nitrogen atom represent a 5- to 10-membered heterocyclic group or an amino group derived from a C_{1-6} alkyl ester of an amino acid, each group being optionally substituted by one or more

substituents selected from the group consisting of halogen atoms, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxycarbonyl, phenyl, halophenyl, C_{1-4} alkylphenyl, C_{1-4} haloalkylphenyl, C_{1-4} alkoxyphenyl, benzyl, pyridyl and pyrimidinyl groups.

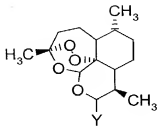
10. (Amended) The method of claim 9, in which Y represents a group $-NR^1R^2$ where R^1 represents a hydrogen atom or a C_{1-4} alkyl group and R^2 represents a C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl or benzyl group, or R^1 and R^2 together with the interjacent nitrogen atom represent a 6- to 10-membered heterocyclic group or an amino group derived from a C_{1-4} alkyl ester of an amino acid, each group being optionally substituted by one or more substituents selected from the group consisting of halogen atoms, C_{1-4} haloalkyl, C_{1-4} alkoxycarbonyl, phenyl, halophenyl, C_{1-4} alkylphenyl, C_{1-4} haloalkylphenyl, C_{1-4} alkoxyphenyl, benzyl, pyridyl and pyrimidinyl groups.

11. (Amended) The method of claim 9, in which Y represents a propylamino, cyclopentylamino, cyclohexylamino, phenylamino, fluorophenylamino, chlorophenylamino, bromophenylamino, iodophenylamino, methoxycarbonylphenylamino, biphenylamino, benzylamino, fluorobenzylamino, bis(trifluoromethyl)benzylamino, phenylethylamino, phenyl-methoxycarbonylmethylamino, diethylamino, morpholinyl, thiomorpholinyl, morpholinosulphonyl, indolinyl, tetrahydroisoquinolinyl, phenylpiperazinyl, fluorophenylpiperazinyl, chlorophenylpiperazinyl, methylphenylpiperazinyl, trifluoromethylphenylpiperazinyl, methoxyphenylpiperazinyl, benzylpiperazinyl, pyridylpiperazinyl and pyrimidinylpiperazinyl group.

12. (Amended) The method of claim 9, in which Y represents a propylamino, phenylamino, bromophenylamino, iodophenylamino, biphenylamino, benzylamino, bis(trifluoromethyl)benzylamino, phenylethylamino, phenyl-methoxycarbonylmethylamino or morpholinyl group.

13. (Amended) The method of claim 1, in which said parasite is an organism of the genus Neospora or the genus Eimeria.

16. (Amended) A compound of the general formula I



(I)

or a salt thereof,

in which

Y represents a halogen atom, an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclylalkyl group or a group $-NR^1R^2$; where

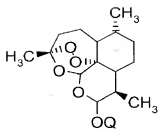
R^1 represents a hydrogen atom or an optionally substituted alkyl, alkenyl or alkynyl group;

R^2 represents an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl group; or

R^1 and R^2 together with the interjacent nitrogen atom represent an optionally substituted heterocyclic group or an amino group derived from an optionally substituted amino acid ester,

with the proviso that, when Y is a group $-NR^1R^2$ and R^2 represents a phenyl, 3-chlorophenyl, 4-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 4-iodophenyl, 4-methylphenyl, 4-methoxyphenyl, 3-carboxylphenyl or 4-carboxylphenyl group, then R^1 is an optionally substituted alkyl group.

17. (Amended) A process for the preparation of a compound of the general formula I according to claim 16 which comprises reacting a compound of the general formula II



(II)

in which Q represents a hydrogen atom or trimethylsilyl group, with a suitable halogenating agent to form a compound of the general formula I in which Y represents a halogen atom.

19. (Amended) A process for the preparation of a compound of the general formula I according to claim 16, in which Y represents an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclylalkyl group which comprises reacting 9,10-anhydroartemisinin with a compound of the general formula Y-H, where Y is as defined above in claim 16, in the presence of a Lewis acid.

20. (Amended) A process for the preparation of a compound of the general formula I according to claim 16, in which Y represents an optionally substituted aryl or C-linked heteroaryl group which comprises reacting 10-trichloroacetimidoyl-10-deoxoartemisinin with a compound of the general formula Y-H, where Y is as defined above in claim 16, in the presence of a Lewis acid.

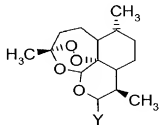
22. (Amended) A process for the preparation of a compound of the general formula I according to claim 16, in which Y represents an optionally substituted aryl or C-linked heteroaryl group which comprises reacting a 10-acyloxyartemisinin compound in which the acyloxy group is of formula A-(C=O)-O-, where A represents an optionally substituted alkyl, cycloalkyl, aryl, aralkyl, heterocyclic or polycyclic group, with a compound of the general formula Y-H, where Y is as defined above in claim 16, in the presence of a Lewis acid.

New Claim for U.S.S.N. 09/743,827 (Attorney Docket No. Le A 33 820)

28. (New) The process of claim 17, further comprising reacting the compound of general formula I thus formed either with a Grignard reagent of the general formula YMgX where Y is an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclylalkyl group and X is a halogen atom to form a compound of general formula I in which Y represents an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclylalkyl group or with an amine of the general formula HNR^1R^2 where R^1 and R^2 are as defined in claim 16 to form a compound of general formula I in which Y represents a group $-NR^1R^2$ where R^1 and R^2 are as defined above in claim 16.

Amended Claims for U.S.S.N. 09/743,827 (Attorney Docket No. Le A 33 820)
Version with Markings to Show Changes Made

1. (Amended) A method of treating or preventing a disease caused by infection with a parasite other than an organism of the genus Plasmodium, comprising administering to a host in need thereof an effective amount of a compound of the general formula I



(I)

or a salt thereof,

in which

Y represents a halogen atom, an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclylalkyl group or a group $-NR^1R^2$; where

R^1 represents a hydrogen atom or an optionally substituted alkyl, alkenyl or alkynyl group;

R^2 represents an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl group; or

R^1 and R^2 together with the interjacent nitrogen atom represent an optionally substituted heterocyclic group or an amino group derived from an optionally substituted amino acid ester[;

for use in the treatment and/or prophylaxis of a disease caused by infection with a parasite other than an organism of the genus Plasmodium].

2. (Amended) The method of [A compound according to] claim 1 in which Y represents a halogen atom.

3. (Amended) The method of [A compound according to claim 1 or] claim 2 in which Y represents a fluorine or bromine atom.

4. (Amended) The method of [A compound according to] claim 1 in which Y represents a C_{3-8} cycloalkyl group, a C_{6-18} aryl group, a 5- to 10-membered C-linked heteroaryl group or a 5- to 10-membered heterocyclyl-C_{1-6} alkyl group, each group being optionally substituted by one or more substituents selected from the group consisting of halogen atoms, hydroxyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, carboxyl, C_{6-10} aryl, 5 to 10-membered heterocyclic and C_{1-4} alkyl- or phenyl-substituted 5- to 10-membered heterocyclic groups.

5. (Amended) The method of [A compound according to] claim 4 in which Y represents a C_{6-18} aryl group optionally substituted by one or more substituents selected from the group consisting of halogen atoms, hydroxyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino and carboxyl groups.

6. (Amended) The method of [A compound according to] claim 4 [or claim 5] in which Y represents a phenyl, naphthyl, anthryl or phenanthryl group, each group being optionally substituted by one or more substituents selected from the group consisting of halogen atoms and hydroxyl, methyl, vinyl, C_{1-4} alkoxy and carboxyl groups.

7. (Amended) The method of [A compound according to any one of] claim[s] 4 [to 6] in which Y represents a phenyl, fluorophenyl chlorophenyl, bromophenyl, trimethylphenyl, vinylphenyl, methoxyphenyl, dimethoxyphenyl, trimethoxyphenyl, carboxylphenyl, naphthyl, hydroxynaphthyl, methoxynaphthyl, anthryl or phenanthryl group.

8. (Amended) The method of [A compound according to any one of] claim[s 4 to] 7 in which Y represents a phenyl or trimethoxyphenyl group.

9. (Amended) The method of [A compound according to] claim 1 in which Y represents a group $-NR^1R^2$ where R^1 represents a hydrogen atom or a C_{1-6} alkyl group and R^2 represents a C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{6-10} aryl or C_{7-16} aralkyl group, or R^1 and R^2 together with the interjacent nitrogen atom represent a 5- to 10-membered heterocyclic group or an amino group derived from a C_{1-6} alkyl ester of an amino acid, each group being optionally substituted by one or more substituents selected from the group consisting of halogen atoms, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxycarbonyl, phenyl, halophenyl, C_{1-4} alkylphenyl, C_{1-4} haloalkylphenyl, C_{1-4} alkoxyphenyl, benzyl, pyridyl and pyrimidinyl groups.

10. (Amended) The method of [A compound according to] claim 9 in which Y represents a group $-NR^1R^2$ where R^1 represents a hydrogen atom or a C_{1-4} alkyl group and R^2 represents a C_{1-4} alkyl, C_{3-6} cycloalkyl, phenyl or benzyl group, or R^1 and R^2 together with the interjacent nitrogen atom represent a 6- to 10-membered heterocyclic group or an amino group derived from a C_{1-4} alkyl ester of an amino acid, each group being optionally substituted by one or more substituents selected from the group consisting of halogen atoms, C_{1-4} haloalkyl, C_{1-4} alkoxycarbonyl, phenyl, halophenyl, C_{1-4} alkylphenyl, C_{1-4} haloalkylphenyl, C_{1-4} alkoxyphenyl, benzyl, pyridyl and pyrimidinyl groups.

11. (Amended) The method of [A compound according to] claim 9 [or claim 10] in which Y represents a propylamino, cyclopentylamino, cyclohexylamino, phenylamino, fluorophenylamino, chlorophenylamino, bromophenylamino, iodophenylamino, methoxycarbonylphenylamino, biphenylamino, benzylamino, fluorobenzylamino, bis(trifluoromethyl)benzylamino, phenylethylamino, phenylmethoxycarbonylmethylamino, diethylamino, morpholinyl, thiomorpholinyl, morpholinosulphonyl, indolinyl, tetrahydroisoquinolinyl, phenylpiperazinyl, fluorophenylpiperazinyl, chlorophenylpiperazinyl, methylphenylpiperazinyl, trifluoromethylphenylpiperazinyl, methoxyphenylpiperazinyl, benzylpiperazinyl, pyridylpiperazinyl and pyrimidinylpiperazinyl group.

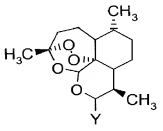
12. (Amended) The method of [A compound according to any one of] claim[s] 9 [to 11] in which Y represents a propylamino, phenylamino, bromophenylamino, iodophenylamino, biphenylamino, benzylamino, bis(trifluoromethyl)benzylamino, phenylethylamino, phenyl-methoxycarbonylmethylamino or morpholinyl group.

13. (Amended) The method of claim 1 [A compound according to any one of the preceding claims] in which the parasite is an organism of the genus Neospora or the genus Eimeria.

14. canceled.

15. canceled.

16. (Amended) A compound of the general formula I



(I)

or a salt thereof,

in which

Y represents a halogen atom, an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclylalkyl group or a group $-NR^1R^2$; where

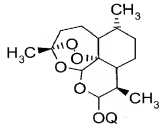
R^1 represents a hydrogen atom or an optionally substituted alkyl, alkenyl or alkynyl group;

R^2 represents an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl group; or

R^1 and R^2 together with the interjacent nitrogen atom represent an optionally substituted heterocyclic group or an amino group derived from an optionally substituted amino acid ester

[as defined in any one of claims 1 to 12,] with the proviso that, when Y is a group -NR^1R^2 and R^2 represents a phenyl, 3-chlorophenyl, 4-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 4-iodophenyl, 4-methylphenyl, 4-methoxyphenyl, 3-carboxylphenyl or 4-carboxylphenyl group, then R^1 is an optionally substituted alkyl group.

17. (Amended) A process for the preparation of a compound of the general formula I according to claim 16 which comprises reacting a compound of the general formula II



(II)

in which Q represents a hydrogen atom or trimethylsilyl group, with a suitable halogenating agent to form a compound of the general formula I in which Y represents a halogen atom[; and, if desired, reacting the compound of general formula I thus formed either with a Grignard reagent of the general formula YMgX where Y is an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclylalkyl group and X is a halogen atom to form a compound of general formula I in which Y represents an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclylalkyl group or with an amine of the general formula HNR^1R^2 where R^1 and R^2 are as defined in claim 13 to form a compound of general formula I in which Y represents a group -NR^1R^2 where R^1 and R^2 are as defined above].

19. (Amended) A process for the preparation of a compound of the general formula I according to claim 16 in which Y represents an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclylalkyl group which comprises

reacting 9,10-anhydroartemisinin with a compound of the general formula Y-H, where Y is as defined above in claim 16, in the presence of a [suitable] Lewis acid.

20. (Amended) A process for the preparation of a compound of the general formula I according to claim [1] 16 in which Y represents an optionally substituted aryl or C-linked heteroaryl group which comprises reacting 10-trichloroacetimidoyl-10-deoxoartemisinin with a compound of the general formula Y-H, where Y is as defined above in claim 16, in the presence of a [suitable] Lewis acid.

22. (Amended) A process for the preparation of a compound of the general formula I according to claim [1] 16 in which Y represents an optionally substituted aryl or C-linked heteroaryl group which comprises reacting a 10-acyloxyartemisinin compound in which the acyloxy group is of formula A- (C=O)-O-, where A represents an optionally substituted alkyl, cycloalkyl, aryl, aralkyl, heterocyclic or polycyclic group, with a compound of the general formula Y-H, where Y is as defined above in claim 16, in the presence of a Lewis acid.

24. canceled.

25. canceled.

26. canceled.

27. canceled.

ANTIPARASITIC ARTEMISININ DERIVATIVES (ENDOPEROXIDES)

This invention relates to the use of certain C-10 substituted derivatives of artemisinin in the treatment and/or prophylaxis of diseases caused by infection with a parasite, certain novel C-10 substituted derivatives of artemisinin, processes for their preparation and pharmaceutical compositions containing such C-10 substituted derivatives.

Malaria is the most important human parasitic disease in the world today. Approximately 270 million people throughout the world are infected with malaria, with about 2 million dying each year. The ability of parasites to produce a complex survival mechanism by expressing variant antigens on the surface of infected erythrocytes makes it possible for the parasites to escape from the destructive action of the host immune response against these antigens. In addition, the increasing rate of malaria infection is due to the spread of chloroquine-resistant strains of Plasmodium falciparum and the other multi-drug resistant strains.

In the field of animal health, parasitic diseases are a major problem, especially those diseases which are functionally related to malaria. For instance, neosporosis is a term used to describe diseases caused by parasites of the species Neospora, especially Neospora caninum, in animals. Neospora infections are known to occur in dogs, cattle, sheep, goats and horses.

The final host for Neospora spp., including Neospora caninum, is unknown and, in addition, the complete cycle of development of the parasite is not understood. The asexual phases of reproduction, known as schizogony, and the behaviour of the unicellular tachyzoite/bradyzoite stage have been clarified, however. Tachyzoites are infectious unicellular parasite stages of about 3-7 x 1-5 mm in size formed

after intracellular reproduction termed endodyogeny. Reproduction via tachyzoites takes place preferentially in organelles such as muscle or nerve cells. Pathological symptoms invoked after an infection are associated mainly in those tissues. Some five to six weeks after natural infection in a dog, symptoms of the disease are hypersensitivity caused by inflammation of neuronal cells and increasing tendency to hyperextension of the hind legs. Histopathological lesions are apparent in the nervous system, preferentially in the brain and spinal cord. Extensive non-suppurative inflammations, glial excrescences and perivascular infiltrations of mononuclear cells (macrophages, lymphocytes, plasma cells) dominate, and are also partly apparent in eosinophils and neutrophils. In the muscular system, macroscopically observable necroses and degenerative changes appear. Apart from the more or less strongly developed atrophy, long pale longitudinal stripes are evident.

In California and Australia, Neospora caninum infections appear to be the main cause for abortion in cattle. Symptoms of the disease in cattle are similar to those in the dog. Ataxia is apparent, joint reflexes are weakened and pareses at the hind legs, partly in all four legs, can be observed. The histological picture is similar to that of the dog; mainly non-suppurative meningitis and myelitis.

Data on in vivo activity of compounds suitable against neosporosis are rare because adequate in vivo test systems still have to be developed. Sulfadiazin (administered via drinking water) is effective in experimentally infected mice, only if the treatment was prophylactic, that is, the treatment was started before infection. In dogs, treatment with sulfadiazin and clindamycin is only successful if it is started early, that is, at the appearance of first clinical

symptoms as a result of neuronal inflammation.

Coccidiosis, an infection of the small intestine, is relatively rarely diagnosed in humans, where it is caused by Isospora belli. However, humans are also the final host of at least two cyst-forming coccidial species (Sarcocystis suihominis and S. bovihominis). Consumption of raw or inadequately cooked pork or beef containing such cysts can lead to severe diarrhoea, the cause of which is probably seldom diagnosed correctly. Coccidia (phylum Apicomplexa, suborder Eimeriina) are one of the most successful groups of parasitic protozoans, having conquered virtually every class of Metazoa. The ones that are of particular importance for man are the 60-100 species which parasitise domestic animals and which in some instances can cause very severe losses, especially in poultry, although also in lambs, calves, piglets, rabbits and other animals (see Table A).

Table A: Causatives of intestinal coccidiosis in domestic animals

Animal	number of Eimeria and/or Isospora species*)	most pathogenic and/or very common species (E=Eimeria, I=Isospora)
chicken (Gallus gallus)	7	E.tenella, E.necatrix, E.maxima, E.acervulina
turkey (Meleagridis gallopavo)	7	E.meleagrimitis, E.adenoides
goose (Anser anser)	6	E.anseris, E.truncata, E.nocens, E. kotlani
duck (Anas platyhynehus)	3	Tyzzeria perniciosa, E.anatis
pigeon (Columba livia)	2	E.columbarum, E.labbeanea
rabbit (Oryctolagus cuniculus)	11(12)	E.intestinalis, E.flavescens, E.stiedai, E.magna, E.perforans
sheep (Ovis arius)	11(16)	E.ovinoidalis,E.ashataE.ovina
goat (Capra hircus)	12(15)	E.ninakohlyakimovae, E.arloingi
cattle (Bos taurus)	12(15)	E.zuernii, E.bovis, E.auburnensis
pig (Sus scofra)	7(14)	I.suis, E.debliecki, E.scabra
dog (Canis familiaris)	5	I.canis, I.(Cystisospora) burrowsi
cat (Felis catus)	2+6	I.felis, I.rivolta as final host: Sarcocystis bovifelis, S.ovifelis, S.fusiformis, S.muris, S.cuniculi. Toxoplasma gondii

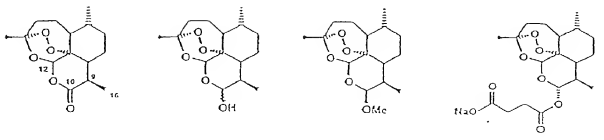
*) regarding to Pellerdy (1974), Eckert et al. (1995b, Levine and Ivens (1970) and Mehlhorn 1988)

Most of the pathogenic species are strictly host-specific. They have a complex life cycle with two asexual reproduction phases (schizogony or merogony, and sporogony) and a sexual development phase (gametogony). In view of the major importance of coccidiosis, numerous reviews are available, for instance, by Davies et al. (1963), Hammond and Long

(1973), Long (1982, 1990), and Pellerdy (1974). The economically important species sometimes differ very considerably in their sensitivity to medicinal active ingredients. The sensitivity of the different developmental stages to medicinal agents also varies enormously.

As far as the use of drugs is concerned, prophylaxis is the main approach in poultry, in which symptoms do not appear until the phase of increased morbidity, and therapy is the principal strategy in mammals (McDougald 1982). Polyether antibiotics and sulfonamides, among other drugs, are currently used for such treatment and prophylaxis. However, drug-resistant strains of Eimeria have emerged and drug-resistance is now a serious problem. New drugs are therefore urgently required. Given the multiplicity of pathogens and hosts, there is no "ideal model" for identifying and testing anticoccidial agents. For example, most of the many substances used for preventing coccidiosis in poultry are insufficiently effective or even completely ineffective against mammalian coccidia (Haberkorn and Mundt; 1989; Haberkorn 1996). Numerous works and sets of instructions have been published on testing of active ingredients in animals for anticoccidial efficacy, for immunisation, etc. One particularly important and comprehensive example is the survey of current methods published by Eckert et al. (1995a).

The compound artemisinin, also known as qinghaosu (1), is a tetracyclic 1,2,4-trioxane occurring in Artemisia annua. Artemisinin and its derivatives dihydroartemisinin (2), artemether (3) and sodium artesunate (4) have been used for the treatment of malaria.



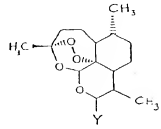
Artemisinin 1 Dihydroartemisinin 2 Artemether 3 Sodium Artesunate 4

Different modes of action have been proposed by various groups to account for the action of artemisinin and its derivatives in treating malaria (Posner et al., *J.Am.Chem.Soc.1996,118,3537*;Posner et al., *J.Am.Chem.Soc.1995,117,5885*;Posner et al., *J. Med.Chem.1995,38,2273*). However, irrespective of actual mode of action, all current derivatives suffer from poor oral bioavailability and poor stability (Meshnick et al., *Parasitology Today 1996,12,79*), especially the 'first generation' ethers and esters artemether and sodium artesunate obtained from dihydroartemisinin. Extensive chemical studies carried out on artemisinin and derivatives indicate that a cause of instability is the facile opening of the trioxane moiety in artemisinin itself, or in the metabolite common to all currently used derivatives artemether, arteether and artesunate, namely dihydroartemisinin. Ring opening will provide the free hydroperoxide, which is susceptible to reduction. Removal of this group ensures destruction of drug activity with the reduction products being transformed into desoxo metabolites. In order to render ring-opening less facile, the oxygen atom at C-10 can be either removed to provide 10-deoxydihydroartemisinin, or replaced by other groups, and this has provided the basis for the so-called 'second generation' compounds which are generally 10-deoxy artemisinin derivatives. In addition, derivatives of artemisinin have also been prepared with a variety of substituents at C-9.

Artemisinin derivatives are also known in which the oxygen atom at C-10 has been replaced by an amine group. For instance, Yang et al (Biorg. Med. Chem. Lett., 1995, 5, 1791-1794) synthesised ten new artemisinin derivatives in which the oxygen atom at C-10 was replaced by a group -NHAr where Ar represents a phenyl, 3-chlorophenyl, 4-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 4-iodophenyl, 4-methylphenyl, 4-methoxyphenyl, 3-carboxylphenyl or 4-carboxylphenyl group. These compounds were tested for in vivo activity against the K173 strain of Plasmodium berghei and found to be active.

Whilst the current artemisinin derivatives are successful, there are problems associated with stability, bioavailability and potential neurotoxicity. There is also a need for artemisinin derivatives which exhibit a broad spectrum of activity against a variety of parasites.

It has now been discovered that certain C-10 substituted derivatives of artemisinin are effective in the treatment of diseases caused by infection with a parasite. These compounds are particularly effective in the treatment of diseases caused by infection with a parasite of the genera Plasmodium, Neospora or Eimeria, especially Plasmodium falciparum, Neospora caninum and Eimeria tenella which cause malaria, neosporosis and coccidiosis respectively. According to the present invention there is therefore provided a compound of the general formula I



(I)

or a salt thereof,
in which
Y represents a halogen atom, an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclylalkyl group or a group $-NR^1R^2$; where
R^1 represents a hydrogen atom or an optionally substituted alkyl, alkenyl or alkynyl group;
R^2 represents an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl group;
or
R^1 and R^2 together with the interjacent nitrogen atom represent an optionally substituted heterocyclic group or an amino group derived from an optionally substituted amino acid ester;
for use in the treatment and/or prophylaxis of a disease caused by infection with a parasite other than an organism of the genus Plasmodium.

Suitable salts include acid addition salts and these may be formed by reaction of a suitable compound of formula I with a suitable acid, such as an organic acid or a mineral acid. Acid addition salts formed by reaction with a mineral acid are particularly preferred, especially salts formed by reaction with hydrochloric or hydrobromic acid. Compounds of formula I in which Y represents a group $-NR^1R^2$ where R^1 and R^2 are as defined above are particularly suitable for the formation of such acid addition salts.

Any alkyl, alkenyl or alkynyl group, unless otherwise specified, may be linear or branched and may contain up to 12, preferably up to 6, and especially up to 4 carbon atoms. Preferred alkyl groups are methyl, ethyl, propyl and butyl. It is preferred that any alkenyl or alkynyl group is not an alk-1-enyl or alk-1-ynyl group. In other words, there should preferably be at least one methylene group $-CH_2-$ or similar sp^3-hybridised centre between a carbon atom forming part of the double or triple C-C bond and the

nitrogen atom to which the group is attached. Preferred alkenyl and alkynyl groups include propenyl, butenyl, propynyl and butynyl groups. When an alkyl moiety forms part of another group, for example the alkyl moiety of an aralkyl group, it is preferred that it contains up to 6, especially up to 4, carbon atoms. Preferred alkyl moieties are methyl and ethyl.

An aryl group may be any aromatic hydrocarbon group and may contain from 6 to 24, preferably 6 to 18, more preferably 6 to 16, and especially 6 to 14, carbon atoms. Preferred aryl groups include phenyl, naphthyl, anthryl, phenanthryl and pyryl groups, especially a phenyl or naphthyl, and particularly a phenyl, group. When an aryl moiety forms part of another group, for example the aryl moiety of an aralkyl group, it is preferred that it is a phenyl, naphthyl, anthryl, phenanthryl or pyryl, especially phenyl or naphthyl, and particularly a phenyl, moiety.

An aralkyl group may be any alkyl group substituted by an aryl group. A preferred aralkyl group contains from 7 to 30, particularly 7 to 24 and especially 7 to 18, carbon atoms, particularly preferred aralkyl groups being benzyl, naphthylmethyl, anthrylmethyl, phenanthrylmethyl and pyrylmethyl groups. A particularly preferred aralkyl group is a benzyl group.

A cycloalkyl group may be any saturated cyclic hydrocarbon group and may contain from 3 to 12, preferably 3 to 8, and especially 3 to 6, carbon atoms. Preferred cycloalkyl groups are cyclopropyl, cyclopentyl and cyclohexyl groups.

A heteroaryl group may be any aromatic monocyclic or polycyclic ring system which contains at least one heteroatom. Preferably, a heteroaryl group is a 5- 18- membered, particularly a 5- to 14-membered, and especially a 5- to 10-membered, aromatic ring system containing at least one heteroatom selected from

oxygen, sulphur and nitrogen atoms. Preferred heteroaryl groups include pyridyl, pyrylium, thiopyrylium, pyrrolyl, furyl, thienyl, indolinyl, isoindolinyl, indolizinyl, imidazolyl, pyridonyl, pyronyl, pyrimidinyl, pyrazinyl, oxazolyl, thiazolyl, purinyl, quinolinyl, isoquinolinyl, quinoxalinyl, pyridazinyl, benzofuranyl, benzoxazolyl and acridinyl groups. A C-linked heteroaryl group is therefore a heteroaryl group as defined above which is linked to the tetracyclic 1,2,4-trioxane moiety of a compound of general formula I via a carbon atom in the heteroaromatic ring system.

A heterocyclic group may be any monocyclic or polycyclic ring system which contains at least one heteroatom and may be unsaturated or partially or fully saturated. The term "heterocyclic" thus includes heteroaryl groups as defined above as well as non-aromatic heterocyclic groups. Preferably, a heterocyclic group is a 3- to 18- membered, particularly a 3- to 14-membered, especially a 5- to 10-membered, ring system containing at least one heteroatom selected from oxygen, sulphur and nitrogen atoms. Preferred heterocyclic groups include the specific heteroaryl groups named above as well as pyranyl, piperidinyl, pyrrolidinyl, dioxanyl, piperazinyl, morpholinyl, thiomorpholinyl, morpholinosulphonyl, tetrahydroisoquinolinyl and tetrahydrofuranyl groups.

A heterocyclylalkyl group may be any alkyl group substituted by a heterocyclic group. Preferably, the heterocyclic moiety is a 3- to 18- membered, particularly a 3- to 14-membered, and especially a 5- to 10-membered, heterocyclic group as defined above and the alkyl moiety is a C_{1-6} alkyl, preferably C_{1-4} alkyl, and especially methyl, group.

An amino acid may be any α-amino acid, such as glycine, alanine, valine, leucine, isoleucine, serine,

threonine, cysteine, cystine, methionine, aspartic acid, glutamic acid, aspargine, glutamine, lysine, hydroxylysine, arginine, histidine, phenylalanine, tyrosine, tryptophan, proline, hydroxyproline or phenylglycine, and includes both D- and L-configurations. An amino acid ester may be any ester of such an amino acid, alkyl esters, particularly C_{1-4} alkyl esters, being especially preferred.

When any of the foregoing substituents are designated as being optionally substituted, the substituent groups which are optionally present may be any one or more of those customarily employed in the development of pharmaceutical compounds and/or the modification of such compounds to influence their structure/activity, stability, bioavailability or other property. Specific examples of such substituents include, for example, halogen atoms, nitro, cyano, hydroxyl, cycloalkyl, alkyl, alkenyl, haloalkyl, alkoxy, haloalkoxy, amino, alkylamino, dialkylamino, formyl, alkoxycarbonyl, carboxyl, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, alkylsulphonato, arylsulphinyl, arylsulphonyl, arylsulphonato, carbamoyl, alkylamido, aryl, aralkyl, optionally substituted aryl, heterocyclic and alkyl- or aryl-substituted heterocyclic groups. When any of the foregoing substituents represents or contains an alkyl or alkenyl substituent group, this may be linear or branched and may contain up to 12, preferably up to 6, and especially up to 4, carbon atoms. A cycloalkyl group may contain from 3 to 8, preferably from 3 to 6, carbon atoms. An aryl group or moiety may contain from 6 to 10 carbon atoms, phenyl groups being especially preferred. A heterocyclic group or moiety may be a 5- to 10-membered ring system as defined above. A halogen atom may be a fluorine, chlorine, bromine or iodine atom and any group which contains a halo moiety, such as a haloalkyl group, may thus

contain any one or more of these halogen atoms.

In one aspect, it is preferred that Y represents a halogen atom, particularly a fluorine or bromine, and especially a fluorine, atom.

In another preferred aspect Y may represent a C_{3-8} cycloalkyl group, a C_{6-18} aryl group, a 5- to 10-membered C-linked heteroaryl group or a 5- to 10-membered heterocyclyl-C_{1-6} alkyl group, each group being optionally substituted by one or more substituents selected from the group consisting of halogen atoms, hydroxyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, carboxyl, C_{6-10} aryl, 5 to 10-membered heterocyclic and C_{1-4} alkyl- or phenyl-substituted 5- to 10-membered heterocyclic groups. Preferably Y represents a C_{6-18} aryl group optionally substituted by one or more substituents selected from the group consisting of halogen atoms, hydroxyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino and carboxyl groups. In particular, Y may represent a phenyl, naphthyl, anthryl or phenanthryl group, each group being optionally substituted by one or more substituents selected from the group consisting of halogen atoms and hydroxyl, methyl, vinyl, C_{1-4} alkoxy and carboxyl groups.

In a particularly preferred sub-group of compounds, Y represents a phenyl, fluorophenyl, chlorophenyl, bromophenyl, trimethylphenyl, vinylphenyl, methoxyphenyl, dimethoxyphenyl, trimethoxyphenyl, carboxylphenyl, naphthyl, hydroxynaphthyl, methoxynaphthyl, anthryl or phenanthryl group. Compounds in which Y represents a phenyl or trimethoxyphenyl group are especially preferred.

In a further preferred aspect, Y may represent a group $-NR^1R^2$ where R^1 represents a hydrogen atom or a

C_{1-6} alkyl group and R^2 represents a C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{6-10} aryl or C_{7-16} aralkyl group, or R^1 and R^2 together with the interjacent nitrogen atom represent a 5- to 10-membered heterocyclic group or an amino group derived from a C_{1-6} alkyl ester of an amino acid, each group being optionally substituted by one or more substituents selected from the group consisting of halogen atoms, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxycarbonyl, phenyl, halophenyl, C_{1-4} alkylphenyl, C_{1-4} haloalkylphenyl, C_{1-4} alkoxyphenyl, benzyl, pyridyl and pyrimidinyl groups. In particular, Y may represent a group $-NR^1R^2$ where R^1 represents a hydrogen atom or a C_{1-4} alkyl group and R^2 represents a C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl or benzyl group, or R^1 and R^2 together with the interjacent nitrogen atom represent a 6- to 10-membered heterocyclic group or an amino group derived from a C_{1-4} alkyl ester of an amino acid, each group being optionally substituted by one or more substituents selected from the group consisting of halogen atoms, C_{1-4} haloalkyl, C_{1-4} alkoxycarbonyl, phenyl, halophenyl, C_{1-4} alkylphenyl, C_{1-4} haloalkylphenyl, C_{1-4} alkoxyphenyl, benzyl, pyridyl and pyrimidinyl groups.

In a particularly preferred sub-group of these compounds, Y represents a propylamino, cyclopentylamino, cyclohexylamino, phenylamino, fluorophenylamino, chlorophenylamino, bromophenylamino, iodophenylamino, methoxycarbonylphenylamino, biphenylamino, benzylamino, fluorobenzylamino, bis(trifluoromethyl)-benzylamino, phenylethylamino, phenylmethoxycarbonyl-methylamino, diethylamino, morpholinyl, thiomorpholinyl, morpholinosulphonyl, indolinyl, tetrahydroisoquinolinyl, phenylpiperazinyl, fluorophenylpiperazinyl, chlorophenylpiperazinyl, methylphenylpiperazinyl, trifluoromethylphenyl-

piperazinyl, methoxyphenylpiperazinyl, benzylpiperazinyl, pyridylpiperazinyl and pyrimidinylpiperazinyl group. Compounds in which Y represents a propylamino, phenylamino, bromophenylamino, iodophenylamino, biphenylamino, benzylamino, bis(trifluoromethyl)benzylamino, phenylethylamino, phenyl-methoxycarbonylmethylamino or morpholinyl group are especially preferred.

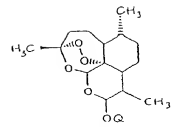
Preferably, the parasite is an organism of the genus Neospora or the genus Eimeria.

The present invention also provides the use of a compound of the general formula I as defined above for the manufacture of a medicament for the treatment and/or prophylaxis of a disease caused by infection with a parasite other than an organism of the genus Plasmodium. Preferably, the parasite is an organism of the genus Neospora or the genus Eimeria.

Certain compounds of the general formula I are novel and the invention therefore further provides a compound of the general formula I as defined above, with the proviso that, when Y is a group $-NR^1R^2$ and R^2 represents a phenyl, 3-chlorophenyl, 4-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 4-iodophenyl, 4-methylphenyl, 4-methoxyphenyl, 3-carboxylphenyl or 4-carboxylphenyl group, then R^1 is an optionally substituted alkyl group.

It should also be appreciated that the compounds of general formula I are capable of existing as different geometric and optical isomers. The present invention thus includes both the individual isomers and mixtures of such isomers.

The present invention also provides a process for the preparation of a novel compound of the general formula I as defined in the ante-preceding paragraph which comprises reacting a compound of the general formula II



(II)

in which Q represents a hydrogen atom or trimethylsilyl group, with a suitable halogenating agent to form a compound of the general formula I in which Y represents a halogen atom; and, if desired, reacting the compound of general formula I thus formed either with a Grignard reagent of the general formula YMgX where Y is an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclylalkyl group and X is a halogen atom to form a compound of general formula I in which Y represents an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclylalkyl group or with an amine of the general formula HNR^1R^2 where R^1 and R^2 are as defined above to form a compound of general formula I in which Y represents a group $-NR^1R^2$ where R^1 and R^2 are as defined above.

Suitable halogenating agents for forming compounds of the general formula I in which Y represents a halogen atom include diethylaminosulphur trifluoride, chlorotrimethylsilane, bromotrimethylsilane and iodotrimethylsilane. In particular, compounds of the general formula I in which Y represents a chlorine, bromine or iodine atom may be prepared by reacting a compound of the general formula II in which Q represents a trimethylsilyl group with a suitable chlorinating, brominating or iodinating agent respectively, such as chlorotrimethlysilane, bromotrimethylsilane or iodotrimethylsilane respectively. This reaction may be conveniently carried out in the presence of a solvent. Suitable solvents include halogenated hydrocarbons, especially chlorinated hydrocarbons, such as dichloromethane.

Preferably, the reaction is carried out at a temperature of -30°C to +10°, particularly -5°C to +5°C, about 0°C being especially preferred.

Compounds of the general formula I in which Y represents a fluorine atom may be conveniently prepared by reacting a compound of the general formula II in which Q represents a hydrogen atom with a suitable fluorinating agent, such as diethylaminosulphur trifluoride. This reaction may be conveniently carried out in the presence of a solvent, suitable solvents including halogenated hydrocarbons, especially chlorinated hydrocarbons, such as dichloromethane. Preferably, the reaction is carried out at -5°C to room temperature, that is, -5 to +35°C, preferably 0 to 30°C. The reaction may also be carried out under an inert atmosphere, such as nitrogen.

Suitable Grignard reagents for forming compounds of the general formula I in which Y is an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclylalkyl group include compounds of the general formula YMgX where X represents a chlorine, bromine or iodine atom. However, it is particularly preferred that X represents a bromine atom. The reaction of a compound of the general formula I in which Y represents a halogen, preferably a bromine, atom with a Grignard reagent may be conveniently carried out in the presence of a solvent. Suitable solvents include ethers, such as diethyl ether. Preferably, the reaction is carried out under an inert atmosphere, such as nitrogen, at a temperature of -5°C to +5°C, 0°C being especially preferred. This method produces a single pure isomer of the final product.

The reaction of an amine with a compound of the general formula I in which Y represents a halogen, preferably a bromine, atom to form a compound of the general formula I in which Y represents a group $-NR^1R^2$

where R^1 and R^2 are as defined above may be conveniently carried out in the presence of a solvent. Suitable solvents include halogenated hydrocarbons, especially chlorinated hydrocarbons, such as dichloromethane, and ethers, such as tetrahydrofuran. Preferably, the reaction is carried out at a temperature of -5°C to +5°C, 0°C being especially preferred.

When a compound of the general formula I in which Y represents a bromine atom is to be further reacted with a Grignard reagent or an amine to form a compound of the general formula I in which Y represents an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclylalkyl group or a group $-NR^1R^2$ where R^1 and R^2 are as defined above, it is preferred that the compound of the general formula I in which Y represents a bromine atom is generated in situ by reacting a compound of the general formula II in which Q represents a trimethylsilyl group with bromotrimethylsilane.

A compound of the general formula II in which Q represents a trimethylsilyl group may be prepared by reacting dihydroartemisinin, that is, the compound of general formula II in which Q represents a hydrogen atom, with chlorotrimethylsilane in the presence of a base, such as pyridine or triethylamine. Preferably, the reaction is carried out at room temperature, that is, 15 to 35°C, preferably 20 to 30°C.

Dihydroartemisinin, that is, the compound of general formula II in which Q represents a hydrogen atom, is a known compound and can be prepared by known processes.

Compounds of the general formula I in which Y represents an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclylalkyl group can also be prepared by reacting 9,10-anhydroartemisinin with a compound of the general formula Y-H, where Y is

as defined above, in the presence of a suitable Lewis acid. This method produces a mixture of isomers in the final product.

Suitable Lewis acids include boron trifluoride dietherate and trifluoromethanesulphonic acid. The reaction may be conveniently carried out in the presence of a solvent. Suitable solvents include halogenated hydrocarbons, especially chlorinated hydrocarbons, such as dichloromethane. Preferably, the reaction is carried out under an inert atmosphere, such as nitrogen, at room temperature, that is, 15 to 35°C, preferably 20 to 30°C.

9,10-Anhydroartemisinin may be conveniently prepared by reacting dihydroartemisinin with trifluoroacetic anhydride. The reaction may be conveniently carried out in the presence of a solvent, preferably a halogenated hydrocarbon, and especially a chlorinated hydrocarbon, such as dichloromethane. It is also preferred that the reaction is carried out in the presence of a base, such as pyridine or a derivative thereof, for example, dimethylamino-pyridine. Preferably, the reaction is carried out under an inert atmosphere, such as nitrogen, at a temperature of -5°C to +5°C, preferably 0°C, with the reaction mixture being subsequently allowed to warm to room temperature, that is, 15 to 35°C, preferably 20 to 30°C.

Compounds of the general formula I in which Y represents an optionally substituted aryl or C-linked heteroaryl group can also be prepared by reacting 10-trichloroacetimidoyl-10-deoxoartemisinin with a compound of the general formula Y-H, where Y is as defined above, in the presence of a suitable Lewis acid, such as boron trifluoride diethyl etherate. It is preferred that the 10-trichloroacetimidoyl-10-deoxoartemisinin is generated in situ by reacting a compound of the general formula II in which Q

represents a hydrogen atom with trichloroacetonitrile in the presence of a suitable base, such as 1,8-diazabicyclo[5.4.0]undecane. Preferably, the reaction to form 10-trichloroacetimidoyl-10-deoxoartemisinin is carried out at room temperature, that is, 15 to 35°C, preferably 20 to 30°C. The reaction may be conveniently carried out in the presence of a solvent. Suitable solvents include halogenated hydrocarbons, especially chlorinated hydrocarbons, such as dichloromethane. Preferably, the remainder of the reaction is carried out under an inert atmosphere, such as nitrogen. Preferably, the remainder of the reaction is carried out at a temperature of -60 to -20°C, particularly -55 to -30°C, and especially -40 to -50°C.

Compounds of the general formula I in which Y represents an optionally substituted aryl or C-linked heteroaryl group can also be prepared by reacting a 10-acyloxyartemisinin compound in which the acyloxy group is of formula A(C=O)-O-, where A represents an optionally substituted alkyl, cycloalkyl, aryl, aralkyl, heterocyclic or polycyclic group, with a compound of the general formula Y-H, where Y is as defined above, in the presence of a suitable Lewis acid. Suitable Lewis acids include boron trifluoride diethyl etherate, tin(IV) chloride, copper(II)-trifluoromethanesulfonate and trifluoromethane-sulphonic acid. It is preferred that the Lewis acid is boron trifluoride diethyl etherate.

When A represents an optionally substituted alkyl group, unless otherwise specified, this may be linear or branched and may contain up to 12, preferably up to 6, and especially up to 4 carbon atoms. Preferred alkyl groups are methyl, ethyl, propyl and butyl.

When A represents an optionally substituted aryl group, this may be any aromatic hydrocarbon group and may contain from 6 to 24, preferably 6 to 18, more preferably 6 to 16, and especially 6 to 14, carbon

atoms. Preferred aryl groups include phenyl, naphthyl, anthryl, phenanthryl and pyryl groups, especially phenyl, naphthyl and anthryl groups. When an aryl moiety forms part of another group, for example the aryl moiety of an aralkyl group, it is preferred that it is a phenyl, naphthyl, anthryl, phenanthryl or pyryl, especially a phenyl or naphthyl, and particularly a phenyl, moiety.

When A represents an optionally substituted aralkyl group, this may be any alkyl group substituted by an aryl group. A preferred aralkyl group contains from 7 to 30, particularly 7 to 24, more particularly 7 to 18, and especially 7 to 10, carbon atoms, particularly preferred aralkyl groups being benzyl, naphthylmethyl, anthrylmethyl, phenanthrylmethyl and pyrylmethyl groups, a benzyl group being especially preferred.

When A represents an optionally substituted cycloalkyl group, this may be any saturated or partially unsaturated cyclic hydrocarbon group and may contain from 3 to 12, preferably 3 to 8, and especially 3 to 6, carbon atoms. Preferred cycloalkyl groups are cyclopropyl, cyclopentyl and cyclohexyl groups.

When A represents an optionally substituted polycyclic group, this may be any saturated or partially unsaturated hydrocarbon group which contains more than one ring system. Such ring systems may be "fused", that is, adjacent rings have two adjacent carbon atoms in common, "bridged", that is, the rings are defined by at least two common carbon atoms (bridgeheads) and at least three acyclic chains (bridges) connecting the common carbon atoms, or "spiro" compounds, that is, adjacent rings are linked by a single common carbon atom. It is also envisaged that a polycyclic group may contain more than one of these types of ring system. Polycyclic groups

preferably contain from 4 to 30, particularly 4 to 26, and especially 6 to 18, carbon atoms. Bicyclic, tricyclic and tetracyclic groups are particularly preferred. Preferred bicyclic groups contain from 4 to 14, especially 6 to 10, carbon atoms. Preferred tricyclic groups contain from 5 to 20, especially 6 to 14, carbon atoms with anthraquinone groups being especially preferred. Preferred tetracyclic groups contain from 6 to 26, especially 6 to 18, carbon atoms.

Optional substituents for the substituent A may be any of those previously identified as suitable in this respect.

The reaction may be conveniently carried out in the presence of a solvent. Suitable solvents include halogenated hydrocarbons, especially chlorinated hydrocarbons, such as dichloromethane. Preferably, the reaction is carried out under an inert atmosphere, such as nitrogen. Preferably, the reaction is carried out at a temperature of -60 to -20°C, particularly -55 to -30°C, and especially -40 to -50°C.

Compounds of formula I in which Y represents a substituted aryl group where at least one of the substituents is a hydroxyl group can also be prepared by rearrangement of the corresponding C-10 ether linked artemisinin derivative so that the oxygen atom of the ether link becomes the oxygen atom of the hydroxyl group in the substituted aryl group of the desired product. Such a rearrangement can be effected by reacting the corresponding C-10 ether linked artemisinin derivative with a Lewis acid, such as a boron trifluoride dietherate. The reaction is conveniently carried out in the presence of a solvent such as dichloromethane at a temperature of -5°C to + 5°C, preferably 0°C.

Certain compounds of the general formula I may also be prepared by conversion of another compound of

general formula I. For instance, 10-(4-vinylphenyl)-dihydroartemisinin may be converted to 10-(4-carboxyphenyl)dihydroartemisinin by reaction with an oxidising agent, such as potassium permanganate. Also, compounds of general formula I which contain a heterocyclic moiety having at least one sulphur atom in the ring system may be oxidised to form compounds of general formula I in which the or each sulphur atom has been converted to a sulphinyl or sulphonyl group by reaction with a suitable oxidising agent. Suitable oxidising agents include 4-methylmorpholine N-oxide (NMO), tetrapropylammonium perruthenate (TPAP) and mixtures thereof. The reaction may be conveniently carried out in the presence of a solvent, suitable solvents including halogenated hydrocarbons, especially chlorinated hydrocarbons, such as dichloromethane. Preferably, the reaction is carried out at room temperature, that is, 15 to 35°C, preferably 20 to 30°C. The reaction may also be carried out under an inert atmosphere, such as nitrogen.

The invention also provides a pharmaceutical composition which comprises a carrier and, as active ingredient, a novel compound of the general formula I as defined above.

A pharmaceutically acceptable carrier may be any material with which the active ingredient is formulated to facilitate administration. A carrier may be a solid or a liquid, including a material which is normally gaseous but which has been compressed to form a liquid, and any of the carriers normally used in formulating pharmaceutical compositions may be used. Preferably, compositions according to the invention contain 0.5 to 95% by weight of active ingredient.

The compounds of general formula I can be formulated as, for example, tablets, capsules,

suppositories or solutions. These formulations can be produced by known methods using conventional solid carriers such as, for example, lactose, starch or talcum or liquid carriers such as, for example, water, fatty oils or liquid paraffins. Other carriers which may be used include materials derived from animal or vegetable proteins, such as the gelatins, dextrins and soy, wheat and psyllium seed proteins; gums such as acacia, guar, agar, and xanthan; polysaccharides; alginates; carboxymethylcelluloses; carrageenans; dextrans; pectins; synthetic polymers such as polyvinylpyrrolidone; polypeptide/protein or polysaccharide complexes such as gelatin-acacia complexes; sugars such as mannitol, dextrose, galactose and trehalose; cyclic sugars such as cyclodextrin; inorganic salts such as sodium phosphate, sodium chloride and aluminium silicates; and amino acids having from 2 to 12 carbon atoms such as a glycine, L-alanine, L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine and L-phenylalanine.

Auxiliary components such as tablet disintegrants, solubilisers, preservatives, antioxidants, surfactants, viscosity enhancers, colouring agents, flavouring agents, pH modifiers, sweeteners or taste-masking agents may also be incorporated into the composition. Suitable colouring agents include red, black and yellow iron oxides and FD & C dyes such as FD & C blue No. 2 and FD & C red No. 40 available from Ellis & Everard. Suitable flavouring agents include mint, raspberry, liquorice, orange, lemon, grapefruit, caramel, vanilla, cherry and grape flavours and combinations of these. Suitable pH modifiers include citric acid, tartaric acid, phosphoric acid, hydrochloric acid and maleic acid. Suitable sweeteners include aspartame, acesulfame K and thaumatin. Suitable taste-masking agents include

sodium bicarbonate, ion-exchange resins; cyclodextrin inclusion compounds, adsorbates or microencapsulated actives.

For treatment of and prophylaxis against coccidiosis and related parasites, for instance, in poultry, especially in chickens, ducks, geese and turkeys, 0.1 to 100 ppm, preferably 0.5 to 100 ppm of the active compound may be mixed into an appropriate, edible material, such as nutritious food. If desired, the amounts applied can be increased, especially if the active compound is well tolerated by the recipient. Accordingly, the active compound can be applied with the drinking water.

For the treatment of a single animal, for instance, for the treatment of coccidiosis in mammals or toxoplasmosis, amounts of 0.5 to 100 mg/kg body weight active compound are preferably administered daily to obtain the desired results. Nevertheless, it may be necessary from time to time to depart from the amounts mentioned above, depending on the body weight of the experimental animal, the method of application, the animal species and its individual reaction to the drug or the kind of formulation or the time or interval in which the drug is applied. In special cases, it may be sufficient to use less than the minimum amount given above, whilst in other cases the maximum dose may have to be exceeded. For a larger dose, it may be advisable to divide the dose into several smaller single doses.

The invention also includes a novel compound of the general formula I as defined above for use in the treatment and/or prophylaxis of a disease caused by infection with a parasite of the genus Plasmodium and use of a novel compound of the general formula I as defined above for the manufacture of a medicament for the treatment and/or prophylaxis of a disease caused by infection with a parasite of the genus Plasmodium.

Preferred compounds in this respect include compounds of the general formula I in which Y represents a fluorine atom, Y represents a phenyl, dimethoxyphenyl or trimethoxyphenyl group or Y represents a propylamino, fluorophenylamino, biphenylamino, benzylamino, phenylethylamino, phenylmethoxycarbonylmethylamino or diethylamino group.

The invention also provides a method for treating a disease caused by infection with a parasite other than an organism of the genus Plasmodium which comprises administering to a host in need of such treatment a therapeutically effective amount of a compound of the general formula I as first defined above. Preferably, the parasite is an organism of the genus Neospora or the genus Eimeria. A method for treating a disease caused by infection with a parasite of the genus Plasmodium is also provided which comprises administering to a host in need of such treatment a therapeutically effective amount of a novel compound of the general formula I as defined above.

The invention is further illustrated by the following examples.

Example 1

Preparation of 10ß-fluoro-10-deoxo-10-dihydroartemisinin (10ß-fluoro-10-deoxodihydroartemisinin) (Formula I: Y = F)

A solution of dihydroartemisinin (1.136 g, 4 mmol) in dichloromethane (24 ml) was cooled to 0°C under nitrogen and diethylaminosulphur trifluoride (DAST) (0.6 ml, 4.8 mmol) was added. The reaction mixture was allowed to warm up to room temperature and then stirred under nitrogen for 24 hours. The yellow solution was cooled again to 0°C, Na_2CO_3 solution (5%, 20 ml) was added and the mixture was stirred for 2 hours at room temperature. After this the two phases

were separated and the organic layer was washed with 1 molar HCl, 5% $NaHCO_3$ and water and dried over $MgSO_4$. Immediately after evaporating the solvent, the residue was purified twice by flash colum chromatography (10% ethyl acetate/hexane), followed by recrystallisation from hexane (289 mg, 50.5%); ^1H NMR(300 MHz, $CDCl_3$): δ ppm 0.97 (d, $J_{6\text{-}Me,6}$=6.1 Hz, 3 H, 6-CH_3), 1.00 (d, $J_{9\text{-}Me,9}$=7.4 Hz, 3 H, 9-CH_3), 1.13-1.47 (m, 3 H), 1.44 (s, 3 H, 3-CH_3), 1.47-1.72 (m, 4 H), 1.82-1.96 (m, 2 H), 2.05 (ddd, J=14.6 Hz, J=4.9 Hz, J=3.0 Hz, 1 H), 2.39 (td, J=13.5 Hz, J=4.0 Hz, 1 H), 2.64 (dm, $J_{9,F}$=36.1 Hz, 1 H, H-9), 5.60 (dd, $J_{10\text{-}F}$=54.4 Hz, $J_{10,9}$=2.4 Hz, 1 H, H-10), 5.56 (d, J=1.83 Hz, 1 H, H-12); ^{19}F NMR(282 MHz, $CDCl_3$): δ (ppm) = - 136.43 (dd, $J_{F,10}$=54.1 Hz, $J_{F,9}$=36.0 Hz); MS (CI,NH_3): m/z (%) = 304 [M^++NH_4^+] (18), 286 [M^+], 284 [304-HF] (100), 257 (64), 256 (28), 239 (16), 221 (12), 163 (8), 52 (28).

Example 2

Preparation of 10ß-phenyl-10-deoxo-10-dihydro-artemisinin (10ß-(phenyl)dihydroartemisinin) (Formula I : Y = phenyl)

(a) Preparation of 10-(trimethylsiloxy)dihydro-artemisinin (Formula II : Q = -Si(CH_3)$_3$)

Method 1

To a solution of dihydroartemisinin (1.51 g, 5.32 mmol) in pyridine (20 ml) at 0°C under nitrogen was added dropwise chlorotrimethylsilane (5.20 ml, mmol). The mixture was stirred at room temperature for a further 1 hour and poured into ice-water mixture. The solution was extracted with diethyl ether (3x15 ml), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2; 5% ethyl acetate/hexanes) to give 10-(trimethylsiloxy)dihydro-artemisinin as a white solid (1.47 g, 78%). δ_H 5.49 (1H, s, H-12), 5.19 (1H, d, J = 3.05 Hz, H-10), 2.52-2.62 (1H, m, H-9), 2.39 (1H, ddd, J = 17.5, 13.4,

4.01 Hz), 2.04 (1H, ddd, J = 14.5, 4.84, 3.05 Hz), 1.20-1.97 (9H, m), 1.45 (3H, s, H-14), 0.97 (3H, d, J = 6.24 Hz, H-16), 0.87 (3H, d, J = 7.29 Hz, H-15), 0.17 (9H, s, $(CH_3)_3Si$).

Method 2

Preparation of 10α-(trimethylsiloxy)dihydro-artemisinin (Formula II: Q = $-Si(CH_3)_3$)

To a solution of dihydroartemisinin (1.51 g, 5.32 mmol) in dichloromethane (40 ml) at 0°C under nitrogen was added dropwise triethylamine (0.94 ml, 6.65 mmol) and chlorotrimethylsilane (0.84 ml, 6.65 mmol). The mixture was stirred at room temperature for a further 1 hour and poured into ice-water mixture. The aqueous solution was extracted with dichloromethane (2x20 ml). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2; 5% ethyl acetate/hexanes) to give 10α-(trimethylsiloxy)dihydro-artemisinin as a white solid (1.48 g, 78%). δ_x 5.32 (1H, s, H-12), 4.76 (1H, d, J = 9.00 Hz, H-10), 2.25-2.45 (2H, m, H-8, H-9), 2.01 (1H, m, H-4), 1.89 (1H, m, H-5), 1.18-1.79 (8H, m, H-2a, H-2b, H-3a, H-3b, H-6a, H-6b, H-7a, H-7b), 1.31 (3H, s, 1-CH_3) 0.95 (3H, d, J = 5.86 Hz, 9-CH_3), 0.86 (3H, d, J = 7.14 Hz, 5-CH_3), 0.20 (9H, s, Me_3Si) ppm.

(b) Preparation of 10-bromo-10-deoxo-10-dihydroartemisinin (10-bromoartemisinin) (Formula I : Y = Br)

A solution of 10α-(trimethylsiloxy)dihydroartemisinin (372 mg, 1.04 mmol) prepared as described in (a) Method 2 above in dichloromethane (5 ml) at 0° C was treated dropwise with bromotrimethylsilane (140 µl, 1.06 mmol). The mixture was stirred at 0°C for a further 30 minutes to produce 10-bromoartemisinin in situ.

(c) Preparation of 10ß-phenyl-10-deoxo-10-dihydro

-artemisinin (10ß-(phenyl)dihydroartemisinin) (Formula I : Y = phenyl).

The solution prepared in (b) above was concentrated in vacuo. The residue was dissolved in diethyl ether (5 ml). To this solution was added phenylmagnesium bromide (1.40 ml, 2.38 mmol, 1.7M) at 0°C under nitrogen. The mixture was then stirred at 0°C and then allowed to reach room temperature overnight. The solution was then quenched with saturated ammonium chloride solution, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2; 8% ethyl acetate/hexanes to give 10ß-phenyl-10-deoxo-10-dihydroartemisinin (10ß-(phenyl) dihydroartemisinin) (159mg, 45%) as a white solid. Recrystallisation from ether/hexane mixture gave a colourless rectangular crystal. M.p. 122°C; $[\alpha]_D^{20}$ - 36.0°(c 0.47/$CHCl_3$); ν_{max} (film) 2938, 2874, 1494, 1452, 1376, 1208, 1112, 1076, 1058, 1038, 1010, 954, 944, 904, 882, 852, 820, 740, 700; δ_H 7.19-7.34 (5H, m, Ar-H), 5.75 (1H, d, J = 6.70 Hz, H-10), 5.60 (1H, s, H-12), 2.71-2.84 (1H, m, H-9), 2.31-2.42 (1H, m), 1.65-2.12 (5H, m), 1.28-1.60 (5H, m), 1.41 (3H, s, H-14), 1.01 (1H, d, J = 5.77 Hz, H-16), 0.54 (1H, d, J = 7.68 Hz, H-15); δ_C 141.03, 127.67, 126.24, 126.09, 102.22, 90.82, 81.10, 72.99, 51.46, 43.45, 37.46, 36.64, 34.16, 32.08, 25.68, 24.88, 24.71, 19.85, 13.62; m/z (CI, CH_4) 345 (M^++1, 14%), 327 (14), 299 (100); Anal.Calc. for $C_{21}H_{28}O_4$: C, 73.26; H,8.14; Found: C,73.58; H,8.32.

nOe-difference experiment: irradiation of the doublet signal of H-10 at δ 5.75 gave 10% enhancement in the multiplet signal of H-9 at δ 2.75; this showed that the stereochemistry of H-10 and H-9 are syn to each other.

Example 3

Preparation of 10α-(4'-fluorobenzylamino)-10-deoxo-10-

dihydroartemisinin (10α-(4'-fluorobenzylamino)dihydroartemisinin) (Formula I : Y = $-NR^1R^2$; R^1 = H; R^2 = 4-F benzyl)

(a) Preparation of 10α-(trimethylsiloxy)dihydroartemisinin (Formula II : Q = $-Si(CH_3)_3$)

To a solution of dihydroartemisinin (1.51 g, 5.32 mmol) in dichloromethane (40 ml) at 0°C under nitrogen was added dropwise triethylamine (0.94 ml, 6.65 mmol) and chlorotrimethylsilane (0.84 ml, 6.65 mmol). The mixture was stirred at room temperature for a further 1 hour and poured into ice-water mixture. The aqueous solution was extracted with dichloromethane (2x20 ml). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2; 5% ethyl acetate/hexanes) to give 10α-(trimethylsiloxy)dihydroartemisinin as a white solid (1.48 g, 78%). δ_H 5.32 (1H, s, H-12), 4.76 (1H, d, J 9.00 Hz, H-10), 2.25-2.45 (2H, m, H-8, H-9), 2.01 (1H, m, H-4), 1.89 (1H, m, H-5), 1.18-1.79 (8H, m, H-2a, H-2b, H-3a, H-3b, H-6a, H-6b, H-7a, H-7b), 1.31 (3H, s, 1-CH_3) 0.95 (3H, d, J 5.88 Hz, 9-CH_3), 0.86 (3H, d, J 7.14 Hz, 5-CH_3), 0.20 (9H, s, Me_3Si) ppm.

(b) Preparation of 10α-(4'-fluorobenzylamino)-10-deoxo-10-dihydroartemisinin (10α-(4'-fluorobenzylamino)dihydroartemisinin) (Formula I : Y = $-NR^1R^2$; R^1=H; R^2 =4-F-benzyl)

A solution of 10α-(trimethylsiloxy)dihydroartemisinin (214 mg, 0.600 mmol) prepared as described in (a) above in dichloromethane (5 ml) at 0°C was treated dropwise with bromotrimethylsilane (80 μl, 0.600 mmol). The mixture was stirred at 0°C for a further 30 minutes after which it was then transferred by cannula into a solution of 4-fluorobenzylamine (140μl 1.20 mmol) in tetrahydrofuran (5 ml) at 0°C. The mixture was stirred at 0°C and then allowed to reach room temperature overnight. The suspension was washed with saturated

$NaHCO_3$ solution, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2; 15% ethyl acetate/hexanes) to give 10α-(4'-fluorobenzylamino)-10-deoxo-10-dihydroartemisinin (10α-(4'-fluorobenzylamino)-dihydroartemisinin) (76.9 mg, 33%) and 9,10-anhydro-10-deoxoartemisinin (9,10-anhydro-dehydroartemisinin) (84.7mg, 53%), both as white solids. M.p. 45.2-46.3°C; $[\alpha]_D^{20}$-18.2°(c 0.055 $CHCl_3$); δ_H 7.32-7.37 (2H, m, Ar-H), 6.95-7.02 (2H, m, Ar-H), 5.29 (1H, s, H-12), 4.10 (1H, d, J = 13.8 Hz, H-1'), 4.08 (1H, d, J = 9.76 Hz, H-10), 3.91 (1H, d, J =13.8 Hz, H-1'), 2.33-2.42 (2H, m), 1.85-2.07 (3H, m), 1.65-1.77 (2H, m), 1.03-1.75 (5H, m), 1.46 (3H, s, H-14), 0.96 (3H, d, J= 6.02 Hz, H-16), 0.93 (3H, d, J = 7.19 Hz, H15); δ_C 136.42 (d, J = 3.10 Hz), 129.30 (d, J = 7.97 Hz), 114.75 (d, J = 21.1 Hz), 103.90, 91.35, 85.47, 80.60, 51.66, 47.50, 45.82, 37.23, 36.26, 34.03, 32.72, 26.03, 24.61, 21.70, 20.15, 14.06; δ_F -118; m/z (CI, CH_4) 392 (M^++1, 90%), 374 (54), 346 (100), 328 (20), 267 (16), 209 (16), 165 (26), 109 (18). Anal. Calc. for $C_{22}H_{30}NO_4F$: C, 67.50; H, 7.72; N, 3.58; Found: C, 67.51; H, 7.77; N, 3.49.

Example 4

Preparation of 10-(2',4'-dimethoxyphenyl)-10-deoxo-10-dihydroartemisinin (10-(2',4'-dimethoxyphenyl)dihydro-artemisinin (Formula I : Y = 2,4-dimethoxyphenyl)

(a) Preparation of 9,10-anhydro-10-deoxoartemisinin (9,10-anhydroartemisinin)

To a solution of dihydroartemisinin (500mg, 1.86 mmol) in dichloromethane (28 ml) at 0°C under nitrogen was added 4-(N,N-dimethylamino)pyridine (37mg) and trifluoroacetic anhydride (0.79ml, 5.58 mmol). The mixture was allowed to warm to room temperature and stirred overnight. The solution was then concentrated in vacuo. The residue was purified by flash

chromatography (SiO_2; ether:hexane from 0.5:9.5 to 1.5:8.5) to give 9,10-anhydro-10-deoxoartemisinin (9,10-anhydroartemisinin) (180 mg, 25%) as a white solid. M.p. 100°C; $[\alpha]_D^{20.5}$ + 155.74° (c.0.0101 in $CHCl_3$); ν_{max} (film): 2948, 2922, 2862, 2850, 1684, 1432, 1372, 1334, 1198, 1178, 1158, 1142, 1114, 1078, 1028, 1016, 992, 954, 944, 904, 880, 828, 812; δ_H : 6.18 (1H, s, H-10), 5.54 (1H, s, H-12), 2.40 (1H, ddd, J = 17.1, 13.2, 4.14 Hz, H-9), 2.00-2.09 (2H, m), 1.88-1.95 (1H, m), 1.07-1.73 (8H, m), 1.58 (3H, d, J = 1.37 Hz, H-16), 1.42 (3H, s, H-14), 0.98 (3H, d, J = 5.98 Hz, H-15); m/z (EI) : 380 (M^+); Anal.Calc. for $C_{15}H_{22}O_4$: C,67.67; H,8.27; Found: C, 67.63; H, 8.51

(b) Preparation of 10-(2',4'-dimethoxyphenyl)-10-deoxo-10-dihydroartemisinin (10-(2',4'-dimethoxyphenyl)-dihydroartemisinin) (Formula I : Y = 2,4-dimethoxyphenyl)

To a solution of 9,10-anhydro-10-deoxoartemisinin (9,10-anhydroartemisinin) (191 mg, 0.71 mmol) prepared as described in (a) above and 1,3-dimethoxybenzene (130µl, 1.00 mmol) in dichloromethane (10 ml) at room temperature under nitrogen was added boron trifluoride diethyl etherate (2 drops). The solution was stirred for a further 1 hour, and then quenched with 20% hydrochloric acid solution (5 ml). The mixture was extracted with diethyl ether (3 x 20 ml), and the ether extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2; 15% ethyl acetate/hexanes) to give 10-(2',4'-dimethoxyphenyl)-10-deoxo-10-dihydroartemisinin (10-(2',4'-dimethoxyphenyl) dihydroartemisinin) (89.5, 44%) as a white solid. δ_H 7.56 (1H, brd, J = 8.4 Hz, Ar-H), 6.40-6.58 (2H, m, Ar-H), 5.43 (1H, s, H12), 5.42 (1H, s, H-12'), 5.16 (1H, d, J = 10.8 Hz, H-10), 4.96 (1H, d, J = 10.3 Hz, H-10'), 3.82, 3.78 (OMe), 2.37-2.48 (2H, m), 1.05-2.07 (10H, m), 1.63 (3H, s, H-14), 1.34 (3H, s, H-14'), 1.00 (3H, d, J = 6.22 Hz,

H-16'), 0.90-0.93 (3H, m, H-15 & H-16), 0.59 (3H, d, J = 7.22 Hz, H-15'); m/z (CI, NH_3) 422 ($M+NH_4^+$, 26%), 406 (84), 405 (M^++1, 54), 389 (80), 359 (100), 330 (30), 317 (40), 300 (14). Anal.Calc. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97%; Found: C, 68.34; H, 8.09.

Example 5

Preparation of 10α-(2'-hydroxy-1'-naphthyl)dihydroartemisinin (Formula I:Y = 2-OH naphthyl)

(a) Preparation of 10ß-(2'naphthoxy)-dihydroartemisinin

To a solution of dihydroartemisinin (568mg, 2.00 mmol) and 2-naphthol (288 mg, 2.00 mmol) in tetrahydrofuran (10 ml) was added triphenylphosphine (524 mg, 4.00 mmol) and diethyl azodicarboxylate (330μl, 2.00 mmol) at °C under nitrogen. The mixture was stirred at room temperature overnight. The yellow solution was then concentrated in vacuo and the residue purified by flash chromotography (SiO_2; 5% ethyl acetate/hexanes) to give 10ß-(2'-naphthyloxy)dihydroartemisinin (185mg, 23%) as a white solid.

(b) Preparation of 10α-(2'-hydroxy-1'-naphthyl)-dihydroartemisinin

To a solution of 10ß-(2'-naphthoxy)dihydroartemisinin (232mg, 0.564 mmol) prepared as described in (a) above in dichloromethane (10 ml) was added boron trifluoride dietherate (220 μl) at 0°C. The mixture was allowed to warm to room temperature and stirred for a further 30 minutes. The solution was washed with 10% sodium hydrogen carbonate solution (2 x 5 ml), dried ($MgSO_4$) and concentrated in vacuo. The residue was then purified by flash chromatography (SiO_2; 10% ethyl acetate/hexanes) to give 10α-(2'-hydroxy-1'-naphthyl)-dihydroartemisinin as a white solid (72.7 mg). δ_H 8.91 (1H, s, OH), 7.28-7.91 (6H, m, Ar-H), 5.57 (1H, s, H-12), 3.11-3.19 (1H, m), 1.28-2.55 (11H, m), 1.51 (3H, s, H-14), 1.04 (3H, d, J = 5.56 Hz, H-16), 0.63

(3H, d, J = 7.23 Hz, H-16).

Example 6

Preparation of 10α-(4'-thiomorpholino-1'-yl)-10-deoxo-10-dihydroartemisinin (10α-(thiomorpholino)dihydroartemisinin)

(Formula I : Y =thiomorpholino)

Reaction of bromide prepared from 10α-(trimethylsiloxy)dihydroartemisnin (356 mg, 1.00 mmol) as described in Example 3(b) above with thiomorpholine (300 μl, 3.00 mmol) afforded 10α-(thiomorpholino)-dihydroartemisinin (243 mg, 65%) as a white solid after flash chromatography (8% ethyl acetate/hexanes). M.p. 147.0-147.6°C; $[\alpha]_D^{20}$ + 17° (c 0.021/$CHCl_3$); ν_{max} (film) 2924, 2872, 1454, 1418, 1376, 1326, 1278, 1226, 1198, 1184, 1154, 1130, 1100, 1056, 1038, 1018, 988, 940, 926, 880, 850, 828, 756; δ_H 5.23 (1H, s, H-12), 3.93 (1H, d, J=10.21 Hz, H-10), 3.20-3.28 (2H, m), 2.85-2.93 (2H, m), 2.53-2.68 (5H, m), 2.25-2.36 (1H, m), 1.93-2.01 (1H, m), 1.78-1.86 (1H, m), 1.63-1.70 (2H, m), 1.14-1.52 (5H, m), 1.36 (3H, s, H-14), 0.90-1.04 (1H, m), 0.91 (3H, d, J=6.14 Hz, H-16), 0.76 (3H, d, J=7.18 Hz, H-15); δ_C: 103.70, 92.28, 91.42, 80.11, 51.54, 50.39, 45.66, 37.19, 36.14, 34.12, 28.15, 25.84, 24.59, 21.44, 20.15, 13.41; m/z (CI, NH_3) 370 (M^++1, 100), 324 (70), 310 (10): Anal. Calc. for $C_{19}H_{31}NO_4S$: C, 61.76; H, 8.46; N, 3.79%; found C, 62.04; H, 8.39; N, 3.65.

Example 7

Preparation of 10α-(4'-(S,S-dioxothiomorpholin-1'-yl)-10-deoxo-10-dihydroartemisinin (10α-(4'-morpholinosulphonyl)dihydroartemisinin) (Formula I : Y = 4'-(S,S-dioxothiomorpholin-1'-yl) (4-morpholinosulphonyl)

To a solution of 10α-(4'-thiomorpholino)-10-deoxo-10-dihydroartemisinin (10α-(thiomorpholino)-dihydroartemisinin) (388 mg, 1.05 mmol) prepared as

described in Example 6 above in dichloromethane (10 ml) at room temperature under nitrogen was added NMO (369 mg, 3.15 mmol), powdered molecular sieve (525 mg, 4 Å), and TPAP (18.5 mg, cat.). The mixture was stirred at room temperature overnight after which it was filtered through a pad of SiO_2 and the residue was washed with ethyl acetate (3x15 ml). The filtrate was concentrated in vacuo. The residue was then purified by flash chromatography (SiO_2; 35% ethyl acetate/ hexanes) to give 10α-(4'-(S,S-dioxothiomorpholin-1'-yl)-10-deoxo-10-dihydroartemisinin (10α-(4'-morpholinosulphonyl)-dihydroartemisinin) as a white solid (421 mg, 100%). M.p. 152.3-152.7°C; $[\alpha]_D^{20}$ + 13° (c 0.035/$CHCl_3$); ν_{max} (film) 2928, 2872, 1454, 1378, 1308, 1270, 1228, 1198, 1124, 1040, 1018, 976, 940, 878, 846, 826, 752, 704, 666; δ_H: 5.27 (1H, s, H-12), 4.21 (1H, d, J=10.30 Hz, H-10), 3.18-3.46, (8H, m), 2.54-2.62 (1H, m), 2.28-2.36 (1H, m), 1.20-2.02 (9H, m), 1.35 (3H, s, H-14), 0.92-1.06 (1H, m), 0.93 (3H, d, J=5.99 Hz, H-15), 0.78 (3H, J=7.13 Hz, H-16); δ_C: 174.20, 104.09, 91.92, 90.84, 90.04, 51.74, 51.27, 46.88, 45.46, 37.29, 36.02, 34.04, 28.91, 25.76, 24.66, 21.45, 20.10, 13.31; m/z (CI,NH_3) 402 (M^++1, 100), 373 (30), 356 (64), 342 (16), 356 (20); Anal. Calc. for $C_{19}H_{31}NO_5S$: C, 56.84; H, 7.78; N, 3.49; found: C, 56.83; H, 7.82; N, 3.37.

Example 8

Preparation of 10α-(4'-benzylpiperazin-1'-yl)-10-deoxo-10-dihydroartemisinin (Formula I: Y = 4'-benzyl-1'-piperazinyl)

Reaction of the bromide prepared from 10ß-(trimethylsiloxy)dihydroartemisinin (356 mg, 1.00 mmol) as described in Example 3(b) with 1-benzylpiperazine (212.1 µl, 1.22 mmol) afforded 10α-(4'-benzylpiperazin-1'-yl)-10-deoxo-10-dihydroartemisinin (144.3 mg, 40%) as a white solid after flash chromatography (40% ethyl acetate/hexane). M.p.105-106°C; $[\alpha]_D^{20}$ + 10.3°

(c. 0.909 $CHCl_3$); ν_{max} (film): 2954, 2920, 2860, 2802, 1494, 1454, 1376, 1344, 1294, 1270, 1204, 1132, 1114, 1062, 1042, 1016, 986, 942, 924, 880, 852, 824, 738, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.43-7.30 (5H, m, Ar-H), 5.35 (1H, s, H-12), 4.10 (1H, d, J = 10.2 Hz, H-10), 3.62 (1H, d, J = 13.1 Hz, benzylic-H), 3.55 (1H, d, J = 13.1 Hz, benzylic-H), 3.11-3.06 (2H, m), 2.80-2.70 (2H, m), 2.70-2.30 (7H, m), 2.15-2.02 (1H, m), 2.02-1.85 (1H, m), 1.85-1.70 (2H, m), 1.70-1.20 (9H, m), 1.20-1.00 (4H, m), 0.88 (3H, d, J = 7.2 Hz, 6-methyl) ppm; ^{13}C NMR (76 MHz, $CDCl_3$) δ_C 138.3, 129.13, 128.1, 126.9, 103.8, 91.6, 90.4, 80.3, 63.1, 53.5, 51.7, 45.9, 37.4, 36.3, 34.3, 28.5, 26.0, 24.8, 21.6, 20.3, 13.4 ppm; MS (CI, CH_4) m/e 443 (M^++1, 10). Anal. Calcd. for $C_{26}H_{38}N_2O_4$: C, 7056, H, 8.65, N, 6.33; Found: C, 70.24, H, 8.67, N, 6.28.

Example 9

Preparation of 10α-(2'-furyl)-10-deoxo-10-dihydroartemisinin (Formula I: Y = 2-furyl)

Method 1:

To a solution of dihydroartemisinin (284 mg, 1.0 mmol) in dichloromethane (10 mL) at 20 °C was added trichloroacetonitrile (2.0 mL, 20.0 mmol) and one drop of 1,8-diazabicyclo[5.4.0]undecane. The mixture was stirred at 20 °C for 2 hours after which it was concentrated in vacuo at 20 °C. The residue was then taken up in dichloromethane (10 mL) at 0 °C and cooled to -40 °C. The solution was treated sequentially with furan (1.09 mL, 15.0 mmol) and boron trifluoride diethyl etherate (123 μl, 1.0 mmol), and the resulting mixture was stirred at -40 °C for another 30 min. The mixture was quenched with saturated $NaHCO_3$ solution and extracted with dichloromethane (2 x 10 mL). The extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2; 15% ethyl acetate/hexanes) to give the captioned

compound (11.0 mg, 3.3%) as a colourless oil. Analytical sample was obtained from recrystallization from hexanes.

Method 2:

(a) Preparation of 10ß-benzoyloxy-10-dihydroartemisinin (10ß-dihydroartemisinyl benzoate)

To a solution of dihydroartemisinin (568 mg, 2.00 mmol) and benzoic acid (244mg, 2.00 mmol) in tetrahydrofuran at 0°C under nitrogen was added triphenylphosphine (524mg, 2.00 mmol) and diethyl azodicarboxylate (ml). The mixture was allowed to warm to room temperature and stirred overnight. The solution was concentrated in vacuo. Flash chromatography (SiO_2; 10% ethyl acetate/hexanes) gave 10ß-dihydroartemisinyl benzoate as a white solid (419mg, 53%). M.p. 151.4-153.0°C; $[\alpha]_D^{20}$ +119° (c 0.19/$CHCl_3$); ν_{max} (film): 2942, 2872, 1724, 1452, 1378, 1268, 1176, 1114, 1064, 1024, 976, 902, 858, 832, 754, 712; δ_H 7.43-8.03 (5H, m, Ar-H), 6.52 (1H, d, J = 3.43, H-10), 5.58 (1H, s, H-12), 2.91-3.01 (1H, m, H-9), 2.42 (1H, ddd, J = 17.4, 13.3, 3.91 Hz), 1.33-2.10 (10H, m), 1.45 (3H, s, H-14), 1.02 (3H, d, J = 6.11 Hz, H-15), 0.98 (3H, d, J = 7.35 Hz, H-14); δ_C : 165.31, 133.03, 129.96, 129.48, 128.39, 104.30, 95.29, 88.66, 88.63, 80.42, 52.27, 43.84, 37.44, 36.10, 34.43, 29.98, 25.78, 24.50, 24.25, 20.14, 12.50; m/z (EI) : 388 (M^+).

(b) Preparation of 10α-(2'-furyl)-10-deoxo-10-dihydroartemisinin

(Formula I : Y = 2-furyl)

A solution of 10ß-benzoyloxy-10-dihydroartemisinin (193 mg, 0.50 mmol) in dichloromethane (5 mL) at -45 °C was treated sequentially with furan (542 µl, 7.5 mmol) and boron trifluoride diethyl etherate (123 µl, 1.0 mmol). The resulting mixture was stirred at -45 °C for another 1 hr. The mixture was quenched with saturated $NaHCO_3$ solution and extracted with dichloromethane (3 x 10

mL). The extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2; 15% ethyl acetate/hexanes) to give the captioned compound (53.7 mg, 32%) as a colourless oil. M.p. 96-97°C; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.38 (1H, m, H-5'), 6.34-6.30 (2H, m, H-3' & H-4'), 5.38 (1H, s, H-12), 4.46 (1H, d, J = 10.9 Hz, H-10), 2.84 (1H, m), 2.60-2.20 (2H, m), 2.20-1.20 (9H, m), 1.20-0.80 (6H, m), 0.62 (3H, d, J = 7.2 Hz, 6-methyl) ppm; ^{13}C NMR (76 MHz, $CDCl_3$) δ_C 153.2, 142.0, 110.0, 108.3, 104.2, 92.2, 80.4, 76.6, 71.1, 52.0, 45.7, 37.4, 36.3, 34.1, 31.5, 26.1, 24.7, 21.3, 20.3, 13.7 ppm; MS (CI, CH_4) *m/e* 335 (M^++1, 43).

Example 10

Preparation of 10α-(Pyrrol-2'-yl)-10-deoxo-10-dihydroartemisinin (Formula I : Y = 2-pyrrolyl)

A solution of 10ß-benzoyloxy-10-deoxoartemisinin (700.8 mg, 1.80 mmol) prepared as described in Example 9, Method 2(a) in dichloromethane (30 mL) at -50 °C was treated sequentially with pyrrole (624 µl, 9.00 mmol) and boron trifluoride diethyl etherate (332 µl, 2.70 mmol), and then stirred at -50 °C for 1 hr. The mixture was quenched with saturated $NaHCO_3$ solution, and extracted with dichloromethane (3 x 10 mL). The extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2; 30% diethyl ether/hexanes) to give the captioned compound (486.6 mg, 81%) as a colourless oil. $[\alpha]_D^{20}$ + 198.7°(c 0.105 $CHCl_3$); ν_{max} (film): 2924, 2854, 1460, 1376, 1066, 1024, 722 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 8.80 (1H, br s, NH), 6.71 (1H, m, H-5'), 6.04 (2H, m, H-3' & H-4'), 5.39 (1H, s, H-12), 4.47 (1H, d, J = 10.8 Hz), 2.58 (1H, m), 2.50-2.10 (2H, m), 2.10-1.95 (1H, m), 1.93 (1H, m), 1.80-1.68 (2H, m), 1.68-1.15 (7H, m), 1.15-0.80 (4H, m), 0.93 (3H, d, J = 7.1 Hz, 6-methyl) ppm; ^{13}C NMR (76 MHz, $CDCl_3$) δ_C 129.9,

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117.6, 107.2, 106.7, 104.1, 91.9, 80.5, 71.9, 60.2, 51.8, 45.7, 37.2, 36.2, 34.0, 32.9, 25.9, 24.6, 21.2, 20.1, 14.0, 13.9 ppm; MS (CI, butane) m/e 334 (M^++1, 100). Anal. Calcd. for $C_{19}H_{27}NO_4$: C, 68.44, H, 8.16, N, 4.20; Found: C, 68.77, H, 8.56, N, 3.85.

Example 11

Preparation of 10α-(4'-Benzyl-4'-methylpiperazinium-1'-yl)-10-deoxo-10-dihydroartemisinin Iodide Salt (Formula I: Y = 4'-benzyl-4'-methylpiperazinium-1'-yl)

A solution of 10α-(4'-benzylpiperazin-1'-yl)-10-deoxo-10-dihydroartemisinin (272 mg, 0.62 mmol) prepared as described in Example 8 above in a mixture of dichloromethane (1.8 mL) and diethyl ether (5.4 mL) under nitrogen atmosphere at 0 °C was treated dropwise with iodomethane (36.7 μl , 0.59 mmol). The mixture was agitated and allowed to warm to 20 °C gradually overnight. The precipitate was collected and washed with diethyl ether (2 x 5 mL) and dried in high vacuum. It was further purified by recrystallization from methanol/diethyl ether to yield rectangular-plate shaped crystals (87 mg, 24%). M.p. 159-161 °C; $[\alpha]_D^{20}$ + 18.4°(c 0.436 $CHCl_3$); ν_{max} (film): 3448, 2928, 2196, 1457, 1378, 1210, 1133, 1099, 1041, 982, 918, 880, 852, 828, 766, 732, 642 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 8.00-7.60 (2H, d, J = 6.2 Hz, H-2" & H-6"), 7.60-7.35 (3H, m, Ar-H), 5.32 (1H, s, H-12), 5.25-5.05 (2H, m, benzylic-H), 4.13 (1H, d, J = 10.2 Hz, H-10), 3.95-3.55 (4H, m), 3.55-2.90 (9H, m), 2.65-2.20 (2H, m), 2.20-1.15 (14H, m), 1.15-0.87 (4H, m), 0.80 (3H, d, J = 6.9 Hz, 6-methyl) ppm; ^{13}C NMR (76 MHz, $CDCl_3$) δ_C 133.4, 130.6, 129.1, 126.5, 104.0, 91.5, 90.1, 80.1, 67.4, 59.5, 59.3, 51.5, 45.5, 37.2, 36.1, 34.0, 28.4, 25.9, 24.5, 21.5, 20.1, 13.3 ppm

Examples 12 to 61

By processes similar to those described in Examples 1

to 11 above, further compounds according to the invention were prepared as detailed in Table I below. In this table, the compounds are identified by reference to formula I.

Table I

Ex. No.	Y	R^1	R^2	Physical data
12	2,4,6-(-OCH_3)$_3$ phenyl (mixture of isomers)	-	-	White foam. $[\alpha]_D^{20.5}$+49.51° (c. 0.053 in $CHCl_3$); ν_{max} (Neat): 2936, 2872, 1608, 1496, 1456, 1420, 1374, 1330, 1278, 1224, 1204, 1152, 1120, 1050, 1040, 974, 954, 930, 902, 880, 856, 834, 814, 734, 702 cm^{-1}; δ_H 6.10-6.18 (2H, m, Ar-H), 5.46 (1H, s, H12), 5.38 (1H, s, H-12'), 5.31 (1H, d, J = 10.4 Hz, H-10), 5.07 (1H, d, J = 10.9 Hz, H-10'), 3.88, 3.81, 3.80, 3.76 (OMe), 3.36-3.42 (1H, m), 2.35-2.41 (1H, m), 1.05-2.15 (10H, m), 1.63 (3H, s, H-14), 1.39 (3H, s, H-14'), 0.99 (3H, d, J = 6.27 Hz, H-16'), 0.88-0.93 (3H, m, H-15 & H-16), 0.58 (3H, d, J = 7.26 Hz, H-15'); m/z (CI, NH_3) 452 ($M+NH_4^+$, 4%), 436 (16), 435 (M^++1, 12), 419 (100), 389 (74), 347 (28). Anal. Calc. for $C_{34}H_{42}O_7$: C, 66.36; H, 7.83; Found: C, 66.42; H, 7.89
13	2-naphthyl (10ß-isomer)	-	-	White solid. M.p. 145-146°C; $[\alpha]_D^{20}$: -67.8° (c 0.027/$CHCl_3$); ν_{max} (film) 2950, 2874, 1510, 1452, 1376,1208, 1106, 1074, 1040, 1010, 954, 936, 886, 854, 824, 786, 750; δ_H 7.80-7.85 (5H, m, Ar-H), 7.42-7.51 (3H, m, Ar-H), 5.93 (1H, d, J = 6.59 Hz, H-10), 5.67 (1H, s, H-12), 2.81-2.94 (1H, m, H-9), 2.33-2.48 (1H,m), 0.86-2.13 (10H, m), 1.42 (3H, s, H-14), 1.02 (1H, d, J = 6.09 Hz, H-16), 0.55 (1H, d, J = 7.66 Hz, H-15); δ_C 134.85, 127.82, 127.42, 127.12, 125.65, 125.17, 124.84, 124.26, 90.92, 73.04, 51.48, 43.44, 37.48,36.64, 34.15, 32.10, 25.69, 24.89, 24.77, 19.85, 13.65; m/z (CI, CH_4) 395 (M^++1, 16%), 394 (M^+, 32), 362 (44), 349 (84), 331 (16), 304 (20), 291 (20), 182 (100), 168 (60). Anal.Calcd. for $C_{25}H_{30}O_4$: C, 76.11; H, 7.66; found: C, 76.24; H, 7.69.

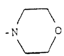
Ex. No.	Y	R^1	R^2	Physical data
14	2-OCH_3 phenyl (10ß-isomer)	-	-	Colourless oil. δ_H 6.83-7.50 (4H, m, Ar-H), 5.94 (1H, d, J = 6.65 Hz, H-10), 5.58 (1H, s, H-12), 3.84 (3H, s, OCH_3), 2.86-2.99 (1H, m, H-9), 2.30-2.40 (1H, m), 1.19-2.11 (10H, m), 1.39 (3H, s, H-14), 1.01 (1H, d, J = 5.77 Hz, H-16), 0.43 (1H, d, J = 7.64 Hz, H-15); δ_C 134.85, 127.00, 126.37, 120.02, 109.19, 90.86, 68.63, 55.19, 51.30, 43.39, 37.53, 36.72, 34.21, 29.87, 25.68, 24.97, 24.75, 19.83, 13.45; m/z (CI, CH_4) 375 (M^++1, 12%), 374 (M^+, 16), 342 (100), 329 (48), 311 (14), 284 (28), 182 (56), 148 (76), 137 (60), 121 (48). Anal.Calc. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.07; Found C, 70.78; H, 8.28
15	$-NR^1R^2$ (10α-isomer)	-H	phenyl	White solid. M.p. 159-160°C; $[\alpha]_D^{20}$ -51.4°(c 0.35/$CHCl_3$); ν_{max} (film) 3348, 2924, 2872, 1604, 1502, 1444, 1376, 1314,1270, 1196, 1152, 1116, 1098, 1040, 1012, 994, 944, 926, 878, 856, 826, 748, 690; δ_H 7.17-7.22 (2H, m, Ar-H), 6.75-6.87 (3H, m, Ar-H), 5.45 (1H, s, H-12), 4.85 (1H, dd, J = 9.86, 9.81 Hz, H-10), 4.32 (1H, d, J = 9.81 Hz, NH), 2.49-2.61 (1H, m, H-9), 2.35-2.45 (1H, m), 2.00-2.08 (1H, m), 1.74-1.92 (4H, m), 1.26-1.65 (7H, m), 1.42 (3H, s, H-14), 1.05-1.10 (1H, m), 1.01 (3H, d, J = 6.18 Hz, H-16), 0.95 (3H, d, J = 7.18 Hz, H-15); δ_C 128.99, 118.56, 114.02, 91.08, 80.70, 80.39, 51.71, 45.76, 37.18, 36.26, 34.03, 32.71, 25.97, 24.60, 21.79, 20.17, 13.80; m/z (CI, CH_4) 360 (M^++1, 56%), 359 (M+, 56), 342 (98), 324 (20), 314 (100), 296 (98), 267 (50), 249 (22), 221 (80), 163 (40), 133 (100), 94 (38). Anal.Calc. for $C_{21}H_{29}NO_4$: C,70.17; H,8.13; N,3.90; Found: C,70.25; H, 8.24; N, 3.73

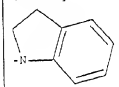
Ex. No.	Y	R^1	R^2	Physical data
16	$-NR^1R^2$ (10α-isomer)	-H	4-F phenyl	White solid. M.p. 170.1°C; ν_{max} (Nujol): 3358 (ν_{NH}), 2924, 2854, 1512, 1460, 1378, 1264, 1216, 1194, 1116, 1099, 1046, 1022, 942, 924, 880, 846, 832, 810, 780 cm^{-1}, δ_H 6.66-6.92 (4H, m, Ar-H), 5.44 (1H, s, H-12), 4.76 (1H, dd, J =10.0, 10.0 Hz, H-10), 4.32 (1H, d, J = 10.0 Hz, NH), 2.49-2.61 (1H, m, H-9), 2.40 (1H, ddd, J = 17.3, 13.4, 3.93 Hz), 2.05 (1H, ddd, J = 14.6, 4.79, 3.07 Hz), 1.05-1.97 (9H, m), 1.42 (3H, s, H-14), 1.00 (3H, d, J = 6.11 Hz, H-16), 0.95 (3H, d, J = 7.10 Hz, H-15); δ_C 141.95, 115.34 (d, J = 17.7 Hz), 115.15 (d, J = 2.69 Hz), 104.13, 91.10 (d,J = 2.22 Hz), 81.41, 80.41, 51.69, 45.73, 37.29, 36.25, 34.01, 32.60, 25.94, 24.60, 21.79, 20.17, 13.81; m/z (CI, CH_4) 378 (M^++1, 44%), 377 (M^+, 100), 358 (70), 314 (14), 267 (26), 221 (18), 163 (34), 151 (42), 111 (6). Anal.Calc. for $C_{21}H_{28}FNO_4$: C,66.82; H,7.48; N,3.71; Found C, 67.06; H, 7.60; N,3.51
17	$-NR^1R^2$ (10α-isomer)	-H	4-Cl phenyl	White solid. M.p. 179.0°C; $[\alpha]_D^{20}$ -63.5° (c 0.20/$CHCl_3$); ν_{max} (film): 3346, 2926, 2874, 1604, 1514, 1494, 1454, 1378, 1268, 1196, 1152, 1094, 1040, 1012, 992, 944, 926, 878, 818, 756; δ_H 7.09-7.14 (2H, m, Ar-H), 6.66-6.71 (2H, m, Ar-H), 5.44 (1H, s, H-12), 4.78 (1H, brs, H-10), 4.42 (1H, brs, NH), 2.49-2.61 (1H, m, H-9), 2.40 (1H, ddd, J = 17.4, 13.5, 3.98 Hz), 2.05 (1H, ddd, J = 14.6, 4.78, 3.12 Hz), 1.05-1.97 (9H, m), 1.41 (3H, s, H-14), 1.00 (3H, d, J = 6.12 Hz, H-16), 0.94 (3H, d, J = 7.18 Hz, H-15); δ_C 144.31, 128.76, 123.20,115.28, 104.15, 91.09, 80.76, 80.38, 51.66, 45.67, 37.28, 36.23, 33.99, 32.56, 25.93, 24.59, 21.78, 20.16, 13.73; m/z (CI, CH_4) 393 (M^++1, 16%), 376 (8), 347 (20), 330 (16), 267 (10), 221 (16), 167 (100), 127 (8). Anal.Calc. for $C_{21}H_{28}ClNO_4$: C, 64.03; H, 7.16; N, 3.55; Found C, 64.16; H, 7.40; N, 3.45.

Ex. No.	Y	R^1	R^2	Physical data
18	$-NR^1R^2$ (10α-isomer)	-H	4-Br phenyl	White solid. M.p. 183.1°C; $[\alpha]_D^{20}$ -60.0° (c 0.23/$CHCl_3$); ν_{max} (film) 3346, 2924, 2872, 1598, 1514, 1492, 1452, 1378, 1268, 1196, 1152, 1122, 1094, 1040, 1012, 992, 926, 878, 816, 756; dH 7.20-7.25 (2H, m, Ar-H), 6.61-6.66 (2H, m, Ar-H), 5.44 (1H, s, H-12), 4.78 (1H, dd, J = 10.0, 9.95 Hz, H-10), 4.48 (1H, d, J = 10.0 Hz, NH), 2.49-2.61 (1H, m, H-9), 2.40 (1H, ddd, J = 14.0, 13.7, 3.87 Hz), 1.05-2.08 (10H, m), 1.41 (3H, s, H-14),1.00 (3H, d, J = 6.07 Hz, H-16), 0.94 (3H, d, J = 7.15 Hz, H-15); δ_C 144.79, 131.61, 115.76, 110.32, 104.17, 91.09, 80.65, 80.39, 51.67, 45.67, 37.29, 36.24, 33.99, 32.54, 25.92, 24.60, 21.78, 20.17, 13.71; m/z (CI, CH_4) 439 (M⁺+1, 12%), 422 (14), 392 (100), 376 (36), 267 (14), 221 (50), 154 (34). Anal.Calc. for $C_{21}H_{31}BrNO_4$: C, 57.54; H, 6.44; N, 3.19; Found: C, 57.81; H, 6.64; N, 3.14.
19	$-NR^1R^2$ (10α-isomer)	-H	4-I phenyl	White solid. $[\alpha]_D^{20}$ -68.8° (c 0.16/$CHCl_3$); ν_{max} (film) 3346, 2924, 1592, 1510, 1454, 1378, 1268, 1196, 1040, 994, 926, 878, 810, 754; δ_H 7.36-7.41 (2H, m, Ar-H), 6.51-6.56 (2H, m, Ar-H), 5.43 (1H, s, H-12),4.78 (1H, dd, J = 10.0, 9.97 Hz, H-10), 4.56 (1H, d, J = 10.0 Hz, NH), 2.34-2.56 (2H, m, H-9), 1.05-2.08 (10H, m), 1.41 (3H, s, H-14), 1.00 (3H, d, J = 6.04 Hz, H-16), 0.93 (3H, d, J = 7.13 Hz, H-15); δ_C 145.46, 137.45, 116.35, 104.18, 91.09, 80.46, 79.59, 51.66, 45.66, 37.29, 36.25, 34.00, 32.50, 25.91, 24.61, 21.79,20.19, 13.71; m/z (CI, CH_4) 486 (M⁺+1, 4%), 485 (M+, 6), 468 (12), 440 (100), 422 (34), 267 (6), 259 (20), 221 (20). Anal.Calc. for $C_{21}H_{31}INO_4$:C, 51.97; H, 5.81; N, 2.89; Found: C, 52.22; H, 5.83; N, 2.57.

Ex. No.	Y	R^1	R^2	Physical data
20	$-NR^1R^2$ (10α-isomer)	-H	4-biphenyl	White solid. $[\alpha]_D^{20}$ -76.5° (c 0.51/$CHCl_3$); ν_{max} (film) 3348, 2924, 2872, 1614, 1528, 1488, 1446, 1378,1268, 1268, 1196, 1152, 1128, 1040, 1012, 992, 926, 878, 826, 760, 698; δ_H 7.25-7.58 (7H, m, Ar-H), 6.82-6.87 (2H, m, Ar-H), 5.49 (1H, s, H-12), 4.90 (1H, dd, J = 9.85, 9.85 Hz, H-10), 4.50 (1H, d, J = 9.85 Hz, NH), 2.36-2.62 (2H, m), 1.07-2.09 (10H, m), 1.44 (3H, s, H-14), 1.02 (3H, d, J = 6.12 Hz, H-16), 0.98(3H, d, J = 7.17 Hz, H-15); δ_C 145.22, 141.16, 131.53, 128.45, 127.71, 126.29, 125.98, 114.30, 104.14, 91.14, 80.67, 80.42, 51.72, 45.76, 37.30, 36.27, 34.04, 21.68, 25.98, 24.62, 21.81, 20.19, 13.81; m/z (CI,CH_4) : 436 (M^++1, 2%), 412 (100), 395 (42), 379 (8), 284 (2), 267 (2), 170 (2). Anal.Calc. for $C_{32}H_{33}NO_4$: C,74.45; H, 7.64; N, 3.22; Found: C, 73.51; H, 7.67; N, 3.12.
21	$-NR^1R^2$ (10α-isomer)	-H	benzyl	White solid. $[\alpha]_D^{20}$ -26.7° (c 0.15/$CHCl_3$); ν_{max} (film) 3348, 2924, 2870, 1452, 1376, 1158, 1116, 1056,1042, 1014, 992, 942, 926, 878, 828, 736, 700; δ_H 7.21-7.42 (5H, m, Ar-H), 5.32 (1H, s, H-12), 4.17 (1H, d, J = 13.9 Hz, H-1'), 4.13 (1H, d, J = 9.63 Hz, H-10), 3.97 (1H, d, J = 13.9 Hz, H-1'), 2.29-2.45 (2H, m), 2.29 (1H, brs, NH), 2.01-2.09 (1H, m), 1.86-1.95 (1H, m), 1.65-1.78 (2H, m), 1.44-1.59 (2H, m), 1.48 (3H, s, H-14), 1.22-1.40 (3H, m), 0.91-1.09 (1H, m), 0.97 (3H, d, J = 5.94 Hz, H-16), 0.96 (3H, d, J = 7.14 Hz, H-15); δ_C 140.82, 128.03, 127.84, 126.45, 103.91, 91.39, 85.68, 80.65, 51.69, 48.21, 45.86, 37.24, 36.29, 34.07, 32.77, 26.07, 24.63, 21.73, 20.19, 14.12; m/z (CI, CH_4) 374 (M^++1, 100%), 356 (54), 338 (42), 328 (38), 309 (12), 253 (16), 221 (10), 119 (16). Anal.Calc. for $C_{23}H_{31}NO_4$: C, 70.75; H, 8.37; N, 3.75; Found; C, 70.78; H, 8.82; N, 3.75.

Ex. No.	Y	R^1	R^2	Physical data
22	$-NR^1R^2$ (10α-isomer)	-H	2-F benzyl	White solid. M.p. 47.4-48.7°C, $[\alpha]_D^{20}$ -16.9° (c 1.46/$CHCl_3$); ν_{max} (film) 3336, 2924, 2872, 1584, 1486, 1454, 1376, 1226, 1196, 1158, 1116, 1056, 1042, 1014, 994, 926, 878, 826, 756; δ_H 6.99-7.50 (4H, m, Ar-H), 5.34 (1H, s, H-12), 4.21 (1H, d, J = 14.5 Hz, H-1'), 4.15 (1H, d, J = 6.72 Hz, H-10), 3.99 (1H, d, J =14.5 Hz, H-1'), 2.35-2.45 (2H, m), 0.90-2.08 (10H, m), 1.47 (3H, s, H-14), 0.98 (3H, d, J= 5.99 Hz, H-16), 0.94 (3H, d, J = 7.16 Hz, H15); δ_C 129.63 (d, J = 4.79 Hz), 127.94 (d, J = 8.05 Hz), 123.64 (d, J = 3.40 Hz), 114.89 (d, J = 21.6 Hz), 103.90, 91.35, 86.03, 80.59, 51.69, 45.86, 41.96 (d, J = 3.53 Hz), 37.26, 36.28, 34.08, 32.66, 26.02, 24.62, 21.72, 20.17, 14.00; δ_F -120; m/z (CI, CH4) 392 (M^++1, 24%), 374 (46), 346 (100), 328 (34), 267 (2), 221 (4), 209 (6), 165 (82), 154 (50), 109 (42). Anal.Calcd. for $C_{22}H_{30}NO_4F$: C, 67.50; H, 7.72; N, 3.58; found C, 67.75, H, 7.92; N, 3.49.
23	$-NR^1R^2$ (10α-isomer)	-H	3,5-$(CF_3)_2$ benzyl	Colourless oil. M.p. 51.0-52.8°C; $[\alpha]_D^{20}$ -27° (c 0.027 $CHCl_3$) δ_H 7.88 (2H, brs, Ar-H), 7.56 (1H, brs, Ar-H), 5.31 (1H, s, H-12), 4.24 (1H, d, J = 15.1 Hz, H-1'), 4.12 (1H, d, J =15.1 Hz, H-1'), 4.06 (1H, d, J = 9.82 Hz, H-10), 2.34-2.45 (2H, m), 0.90-2.09 (10H, m), 1.47 (3H, s, H-14), 0.98 (3H, d, J= 7.26 Hz, H-15), 0.97 (3H, d, J = 4.94 Hz, H16); δ_F -64.1; m/z (CI, CH_4) 510 (M^++1, 48%), 490 (100), 464 (74), 441 (38), 283 (24), 267 (30), 244 (10), 221 (20), 163 (22). Anal. Calc. for $C_{24}H_{29}NO_4F_6$: C, 56.58; H, 5.74; N, 2.75; Found: C, 56.75; H, 5.76; N, 2.70.

Ex. No.	Y	R^1	R^2	Physical data
24	$-NR^1R^2$ (10α-isomer)	-H	$-^nC_3H_7$	White solid. M.p. 96.1-97.3°C (changed colour before melting); $[\alpha]_D^{20}$ +24.8° (c 0.33/$CHCl_3$); ν_{max} (film) 3304, 2952, 2924, 2870, 1492, 1454, 1378, 1208, 1160, 1118, 1042, 1012, 974, 942, 922, 878, 844, 828, 754; δ_H 5.31 (1H, s, H-12), 4.11 (1H, d, J = 9.78 Hz, H-10), 2.95 (1H, ddd, J = 11.4, 8.07, 6.55 Hz, CH_2NH), 2.61 (1H, ddd, J = 11.4, 8.07, 6.45 Hz, CH_2NH), 2.26-2.43 (2H, m), 2.03 (1H, ddd, J = 14.5, 4.54, 2.49 Hz), 1.84-1.93 (1H, m), 1.00-1.83 (10H, m), 1.44 (3H, s, H-14), 0.97 (3H, d, J = 6.10 Hz, H-16), 0.92 (3H, t, J = 7.36 Hz, CH3), 0.89 (3H, d, J = 7.18 Hz, H-15); δ_C 103.82, 91.34, 86.17, 51.69, 46.27, 45.88, 37.27, 36.27, 34.10, 32.49, 26.04, 24.61, 23.49, 21.72, 20.19, 14.03, 11.62; m/z (CI, CH_4) 326 (M^++1, 100%), 308 (56), 280 (48), 221 (16), 163 (18). Anal.Calcd. for $C_{18}H_{33}NO_4$: C, 66.43; H, 9.60; N, 4.36; Found: C, 66.17, H, 9.68; N, 4.20.
25	morpholino  (10α-isomer)	-	-	White solid. M.p. 121.2°C; $[\alpha]_D^{20}$ +15.3° (c 0.30/$CHCl_3$); ν_{max} (film) 2924, 2850, 1450, 1376, 1294, 1258, 1202, 1158, 1110, 1056, 984, 930, 880, 846, 826, 744; δ_H 5.29 (1H, s, H-12), 3.99 (1H, d, J = 10.23 Hz, H-10), 3.63-3.76 (4H, m, $O(CH_2)_2$), 2.96-3.03 (2H, m, $\underline{CH_2}NC\underline{H_2}$), 2.64-2.71 (2H, m, $\underline{CH_2}NCH_2$), 2.53-2.61 (1H, m, H-9), 2.31-2.41 (1H, m), 1.00-2.06 (10H, m), 1.41 (3H, s, H-14), 0.96 (3H, d, J = 6.14 Hz, H-16), 0.83 (3H, d, J = 7.18 Hz, H-15); δ_C 103.74, 91.48, 90.51, 80.16, 67.25, 51.57, 47.52, 45.66, 37.25, 36.16, 34.14, 28.04, 25.84, 24.62, 21.50, 20.14, 13.25; m/z (EI) 353 (M+, 6), 294 (4), 236 (4), 221 (16), 209 (12), 163 (14), 127 (32), 116 (100), 88 (24). Anal.Calcd. for $C_{19}H_{31}NO_5$: C, 64.56; H, 8.84; N, 3.96%; Found: C, 64.67; H, 9.10; N, 3.90.

Ex. No.	Y	R^1	R^2	Physical data
26	$-NR^1R^2$ (10α-isomer)	$-C_2H_5$	$-C_2H_5$	White solid. δ_H 5.37 (1H, s, H-12), 4.76 (d, J = 7.54 Hz, H-10), 2.80-3.03 (4H, m, $N(CH_2CH_3)_2$), 2.29-2.44 (1H, m, H-9), 0.94-1.89 (11H, m), 1.53 (3H, s, H-14), 1.14 (6H, dd, J = 7.20, 7.12 Hz, $N(CH_2CH_3)_2$), 1.04 (3H, d, J = 7.23 Hz, H-15), 0.91 (3H, d, J = 5.72 Hz, H-16); δ_C 105.33, 96.11, 81.43, 51.68, 45.23, 41.48, 35.12, 34.52, 33.96, 25.56, 23.77, 22.24, 21.88, 18.52, 15.56, 11.50. m/z (CI, CH_4) : 340 (M^++1, 52%), 251 (100), 221 (26).
27	indolinyl  (10α-isomer)	-	-	White solid. M.p. 147.8-148.2°C; $[\alpha]_D^{26}$ -11.6° (c 0.19/$CHCl_3$); ν_{max} (film) 2926, 2872, 1606, 1488, 1462, 1376, 1258, 1200, 1158, 1126, 1040, 1010, 926, 880, 828, 746, 718; δ_H 7.03-7.09 (2H, m, Ar-H), 6.60-6.71 (2H, m, Ar-H), 5.44 (1H, s, H-12), 4.98 (1H, d, J = 10.4 Hz, H-10), 3.79 (1H, apparent dt, J = 10.4, 9.08 Hz, $ArCH_2$), 3.56 (1H, apparent dt, J = 9.08, 4.36 Hz, $ArCH_2$), 2.94-3.12 (2H, m, NCH_2), 2.67-2.79 (1H, m, H-9), 2.39 (1H, ddd, J = 14.3, 13.3, 3.94 Hz), 2.03 (1H, ddd, J = 14.5, 4.73, 2.97 Hz), 1.75-1.95 (4H, m), 1.06-1.69 (6H, m), 1.38 (3H, s, H-14), 1.00 (3H, d, J = 6.17 Hz, H-16), 0.94 (3H, d, J = 7.16 Hz, H-15); δ_C 150.51, 130.18, 126.92, 124.57, 118.19, 107.47, 103.90, 91.46, 81.53, 80.05, 51.58, 45.61, 44.83, 37.28, 36.20, 34.12, 29.75, 27.99, 25.83, 24.61, 21.51, 20.16, 13.30; m/z (CI, CH_4) 336 (M^++1, 100), 340 (50), 326 (14), 267 (6). Anal.Calcd. for $C_{21}H_{31}NO_4$: C, 71.66; H, 8.10; N, 3.63; Found: C, 71.45; H, 8.07; N, 3.57.

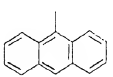
Ex. No.	Y	R^1	R^2	Physical data
28	1,2,3,4-tetrahydro-isoquinolinyl  (10α-isomer)	-	-	White solid. M.p. 125.3-126.6°C; $[\alpha]_D^{25}$ +14.7° (c 0.19/$CHCl_3$); ν_{max} (film) 2924, 2870, 1452, 1376, 1278, 1200, 1154, 1130, 1100, 1040, 1014, 982, 926, 880, 826, 742; δ_H 7.07-7.15 (4H, m, Ar-H), 5.36 (1H, s, H-12), 4.26 (1H, d, J = 10.2 Hz, H-10),4.20 (1H, d, J = 15.2 Hz, $ArCH_2N$), 3.97 (1H, d, J = 15.2 Hz, $ArCH_2N$), 3.26-3.36 (1H, m, $ArCH_2$), 2.70-3.00 (4H, m, 3H-CH_2CH_2N & 1H), 2.40 (1H, ddd, J = 14.4, 13.6, 3.93 Hz), 2.00-2.07 (1H, m),1.86-1.95 (1H, m), 1.71-1.81 (2H, m), 1.19-1.65 (4H, m), 1.41 (3H, s, H-14), 1.02-1.12 (1H, m), 0.99 (3H,d, J = 6.09 Hz, H-16), 0.87 (3H, d, J = 7.19 Hz, H-15); δ_C 135.74, 134.94, 128.55, 126.59, 125.45, 125.21, 103.76, 91.61, 90.60, 80.31, 51.64, 49.18, 45.82, 45.65, 37.29, 36.21, 34.20, 29.89, 28.66, 25.88, 24.67, 21.53, 20.19, 13.46; m/z (CI, CH_4) 400 (M+1, 100), 398 (22), 354 (54), 340 (20), 267 (4), 162 (44), 134 (14). Anal.Calc. for $C_{24}H_{33}NO_4$: C, 72.15; H, 8.33; N, 3.51: Found: C, 71.98; H, 8.36; N, 3.36.
29	$-NR^1R^2$ (10α,1'S-isomer)	-H	-CH(phenylCH_3)	White solid. M.p. 55.4-57.5°C; δ_H 7.20-7.42 (5H, m, Ar-H), 5.13 (1H, s, H-12), 4.45 (1H, q, J = 6.62 Hz, H-1'), 3.77 (1H, d, J = 9.79 Hz, H-10), 2.23-2.43 (2H, m), 2.03 (1H, ddd, J = 14.5, 4.73, 3.08 Hz), 0.96-1.88 (9H, m), 1.48 (3H, s, H-14), 1.31 (3H, d, J = 6.62 Hz, CH_3), 0.91 (3H, d, J = 5.94 Hz, H-16), 0.91 (3H, d, J = 7.14 Hz, H-15); δ_C 146.07, 128.01, 126.96, 126.39, 103.81, 91.38, 83.80, 80.70, 52.37, 51.71, 45.82, 37.00, 36.30, 33.95, 33.40, 26.11, 25.53, 24.57, 21.64, 20.14, 14.22; m/z (CI, CH_4) 388 (M+1, 100%), 370 (22), 342 (64), 267 (8), 221 (10). Anal.Calc. for $C_{23}H_{33}NO_4$: C,71.29; H, 8.58; N, 3.61; Found C, 71.20; H, 8.72; N, 3.62.

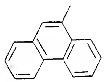
Ex. No.	Y	R^1	R^2	Physical data
30	$-NR^1R^2$ (10α,1'R-isomer)	-H	-CH(CH$_3$)phenyl	White solid. δ_H 7.20-7.43 (5H, m, Ar-H), 5.16 (1H, s, H-12), 4.44 (1H, q, J = 6.41 Hz, H-1'), 4.31 (1H, d, J = 9.70 Hz, H-10), 2.21-2.40 (2H, m), 2.00-2.08 (1H, m), 1.02-1.95 (9H, m), 1.45 (3H, s, H-14), 1.31 (3H, d, J = 6.41 Hz, CH$_3$), 0.99 (3H, d, J = 6.18 Hz, H-16), 0.93 (3H, d, J = 7.16 Hz, H-15); δ_C 147.01, 128.06, 127.01, 126.59, 103.85, 91.33, 83.03, 80.56, 51.72, 51.51, 45.92, 37.29, 36.28, 34.14, 33.09, 26.01,24.66, 22.35, 21.83, 20.21, 14.22; m/z (CI, CH$_4$) 388 (M$^+$+1, 100%), 370 (56), 342 (42), 309 (30), 267 (18),253 (32), 221 (20), 119 (34).
31	$-NR^1R^2$ (10α,1'R-isomer)	-H	-CH(CO-OCH$_3$)phenyl	Colourless oil. ν_{max} (Neat): 3342 (ν_{NH}), 2926, 2827, 1742 ($\nu_{C=O}$, ester), 1602, 1494, 1452, 1376, 1246, 1198, 1158, 1130, 1042, 1014, 994, 928, 880, 844, 826, 736, 700 cm^{-1}; ^{1}H nmr (300 MHz, CDCl$_3$) δ_H 7.21-7.50 (5H, m, Ar-H), 5.13 (1H, s, H-12), 4.94 (1H, s, H-2'), 3.85 (1H, d, J 9.81 Hz, H-10), 3.65 (3H, s, OMe), 2.74 (1H, br.s., NH), 2.35 (1H, m, H-9), 1.05-2.07 (11H, m, H-2 x 2, H-3 x 2, H-4, H-5, H-6 x 2, H-7 x 2, H-8), 1.47 (3H, s, 1-CH$_3$), 0.90 (6H, d x 2, signals overlap, 5-CH$_3$, 9-CH$_3$) ppm; m/z (CI, CH$_4$) 432 (M$^+$+1, 96%), 386 (100), 372 (44), 312 (14), 267 (24), 221 (28), 166 (96). Anal.Calcd. for $C_{24}H_{33}NO_4$: C, 66.80; H, 7.71; N, 3.24; Found: C, 66.98; H, 7.53; N, 3.05.
32	$-NR^1R^2$ (10α,1'S-isomer)	-H	-CH(CO-OCH$_3$)phenyl	^{1}H nmr (300 MHz, CDCl$_3$) δ_H 7.28-7.51 (5H, m, Ar-H), 5.22 (1H, s, H-12), 5.04 (1H, s, H-2'), 4.28 (1H, d, J 9.81 Hz, H-10), 3.60 (3H, s, OMe), 2.57 (1H, br.s., NH), 2.29-2.44 (1H, m, H-9), 0.96-2.44 (11H, m, H-2 x 2, H-3 x 2, H-4, H-5, H-6 x 2, H-7 x 2, H-8), 1.43 (3H, s, 1-CH$_3$), 0.97 (3H, d, J 6.11 Hz, H-15), 0.90 (3H, d, J 7.16 Hz, H-16)ppm; m/z (CI, CH$_4$) 432 (M$^+$+1, 90%), 386 (100), 372 (50).

Ex. No.	Y	R^1	R^2	Physical data
33	$-NR^1R^2$ (10α-isomer)	-H	4-(CO-OCH$_3$)phenyl	White solid. M.p. 117.7-118.5°C; $[\alpha]_D^{20}$ -84.1 (c 0.82/$CHCl_3$); ν_{max} (film) 3344, 2948, 1710, 1608, 1528, 1434, 1378, 1270, 1178, 1110, 1040, 1012, 926, 878, 842, 768; δ_H 6.66-7.76 (4H, m, Ar-H), 5.46 (1H, s, H-12), 5.06 (1H, d, J=9.96 Hz, NH), 4.88 (1H, dd, J=9.89, Hz, H-10), 3.83 (3H, s, OMe), 2.56-2.60 (1H, m), 2.33-2.42 (1H, m), 0.85-2.04 (10H, m), 1.39 (3H, s, H-14), 0.99 (3H, d, J=6.09 Hz, H-15), 0.92 (3H, d, J=7.11 Hz, H-16; δ_C: 167.06, 149.99, 131.04, 119.64, 113.01, 104.30, 91.21, 80.49, 80.02, 51.70, 51.40, 45.67, 37.34, 36.20, 34.04, 32.50, 25.92, 24.66, 21.84, 20.94, 20.22, 14.10, 13.67; m/z (CI, CH_4) 418 (M^++1,32), 400 (6), 372 (100), 358 (8), 221 (20), 152 (26). Anal.Calc. for $C_{23}H_{31}NO_6$: C,66.17; H,7.48; N, 3.35; Found: C,65.57; H,7.57; N, 3.36.
34	$-NR^1R^2$ (α-isomer)	-H	cyclopentyl	White solid. M.p. 114.1-114.9°C; $[\alpha]_D^{25}$: -1.6°(c 0.98/$CHCl_3$); ν_{max} (film) 3314, 2950, 2870, 1446, 1376, 1198, 1154, 1114, 1098, 1042, 1014, 976, 944, 924, 878, 860, 826, 754; δ_H: 5.29 (1H, s, H-12), 4.08 (1H, d, J=9.76 Hz, H-10), 3.52-3.60 (1H, m, H-1'), 2.23-2.41 (2H, m), 1.24-2.05 (17H, m), 1.43 (3H, s, H-14), 0.84-1.11 (1H, m), 0.96 (3H, d, J=6.15 Hz, H-15), 0.85 (3H, d, J=7.17 Hz, H-16); δ_C 103.91, 91.44, 85.08, 80.77, 54.33, 51.84, 46.01, 37.38, 36.40, 34.23, 34.20, 33.11, 32.70, 26.17, 24.74, 23.63, 21.89, 20.31, 14.30; m/z (CI, CH_4) 352 (M^++1, 14), 334 (10), 306 (100), 288 (14), 251 (4), 221 (4), 125 (10); Anal.Calc. for $C_{20}H_{33}NO_4$: C, 68.34, H, 9.46; N, 3.98; Found: C, 67.89; H, 9.46; N, 3.92

Ex. No.	Y	R^1	R^2	Physical data
35	$-NR^1R^2$ (α-isomer)	-H	cyclohexyl	White solid. δ_H 5.28 (1H, s, H-12), 4.17 (1H, d, J= 9.69 Hz, H-10), 2.93-3.00 (1H, m H-1'), 2.16-2.41 (2H, m), 0.84-2.03 (19H, m), 1.42 (3H, s, H-14), 0.95 (3H, d, J=6.11 Hz, H-15), 0.85 (3H, d, J=7.18 Hz, H-16); δ_C 103.87, 91.36, 83.36, 80.70, 51.84, 50.94, 46.04, 37.36, 36.38, 34.58, 34.21, 33.18, 32.79, 26.29, 26.12, 24.75, 24.71, 24.27, 21.88, 20.29, 14.25, 14.19; m/z (CI, CH_4) 366 (M^++1, 10), 348 (10), 329 (100), 318 (12), 221 (4), 139 (8); Anal.Calcd. for $C_{21}H_{31}NO_4$; C, 69.01; H, 9.65; N, 3.83; found: C, 68.85, H, 9.85; N, 3.80.
36	N-methyl-piperazino  (10α-isomer)	-	-	Brownish yellow solid. M.p. 112-114°C; $[\alpha]_D^{20}$-12.95° (c.0.0149 in $CHCl_3$); ν_{max} (Neat): 2934, 2872, 2792, 1454, 1376, 1286, 1226, 1192, 1162, 1132, 1102, 1054, 1014, 984, 926, 880, 830 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ_H 5.26 (1H, s, H-12), 4.02 (1H, d, J 10.20 Hz, H-10), 3.03 (2H, m, H-6'a, H-6'b), 2.70 (2H, m, H-2'a, H-2'b), 2.59 (1H, m, H-9), 2.30-2.50 (5H, m, H-8, H-3'a, H-3'b, H-5'a, H-5'b), 2.28 (3H, s, N-Me), 1.18-2.05 (10H, m, H-2a, H-2b, H-3a, H-3b, H-4, H-5, H-6a, H-6b, H-7a, H-7b), 1.16 (3H, s, 1-CH_3), 0.94 (3H, d, J 6.12 Hz, 9-CH_3), 0.80 (3H, d, J 7.17 Hz, 5-CH_3) ppm; δ_C 104.46, 92.16, 90.96, 90.88, 56.18, 52.36, 46.82, 38.05, 36.96, 34.97, 29.16, 26.55, 25.46, 22.30, 20.96, 14.03; m/z (CI, CH_4) 367 ([M+1]$^+$, 100), 321 ([M-3CH_3]$^+$,26).m/z (CI, CH_4) 367 ([M+1]$^+$, 100), 321 ([M-3CH_3]$^+$,26).

Ex. No.	Y	R^1	R^2	Physical data
37	4-vinylphenyl (10ß-isomer)	-	-	White solid. $[\alpha]_D^{22}$-64.6° (c 0.028/$CHCl_3$); ν_{max} (film) 2948, 2876, 1630, 1512, 1452, 1406, 1376, 1200, 1116, 1074, 1010, 944, 904, 882, 844, 788, 756; δ_H : 7.37 (2H, d, J=8.26 Hz, Ar-H), 7.27 (2H, d, J=8.26 Hz, Ar-H), 6.71 (1H, dd, J=17.62, 10.90 Hz, vinyl-H), 5.69-5.76 (2H, m, vinyl-H, H-10), 5.57 (1H, s, H-12), 5.20 (1H, d, J=10.90 Hz, vinyl-H), 2.71-2.78 (1H, m), 2.28-2.38 (1H, m), 1.17-2.09 (9H, m), 1.38 (3H, s, H-14), 0.83-0.99 (1H, m), 0.98 (3H, d, J=5.74 Hz, H-15), 0.54 (3H, d, J=7.67 Hz, H-16); δ_C: 140.91, 136.75, 135.74, 126.36, 125.72, 113.09, 102.40, 90.89, 81.24, 73.07, 51.58, 43.58, 37.58, 36.73, 34.26, 32.19, 25.80, 24.98, 24.80, 19.97, 13.75. Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16; found: C, 74.58; H, 8.26.
38	4-Br phenyl (10ß-isomer)	-	-	White rectangular crystal. M.p. 156-159°C; $[\alpha]_D^{20.5}$-45.14° (c 0.0216 in $CHCl_3$); ν_{max} (Nujol): 2924, 1492, 1454, 1374, 1112, 1008, 942, 902, 882, 840, 780 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δH 7.43 (2H, d, J 8.40 Hz, H-3', H-5'), 7.19 (2H, d, J 8.40 Hz, H-2', H-6'), 5.70 (1H, d, J 6.60 Hz, H-10), 5.55 (1H, s, H-12), 2.72 (1H, m, H-9), 2.33 (1H, m, H-8), 1.19-2.10 (10H, m, H-2a, H-2b, H-3a, H-3b, H-4, H-5, H-6a, H-6b, H-7a, H-7b), 1.40 (3H, s, 1-CH_3), 0.98 (3H, d, J 5.70 Hz, 9-CH_3), 0.48 (3H, d, J 7.80 Hz, 5-CH_3) ppm; m/z (CI, CH_4) 453 ([M(Br^{81})+2CH_4]$^+$,18), 451 ([M(Br^{79})+2CH_4]$^+$,20), 425 ([M(Br^{81})+1]$^+$,51), 423([M(Br^{79})+1]$^+$,53), 407 (40), 405 (32), 392 (35), 390 (48), 379 (100), 377 (88), 335 (20), 333 (28), 267 (32), 221 (41), 209 (78), 191 (78), 191 (26), 163 (59).

Ex. No.	Y	R^1	R^2	Physical data
39	4-Cl phenyl (10ß-isomer)	-	-	White rectangular crystal. M.p. 161-146°C; $[\alpha]_D^{20.5}$-10.35° (c 0.0508 in $CHCl_3$); ν_{max} (Nujol): 2924, 1494, 1456, 1374, 1114, 1008, 942, 902, 840, 782 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ_H 7.30 (2H, d, J 8.16 Hz, H-3', H-5'), 7.24 (2H, d, J 8.16 Hz, H-2', H-6'), 5.69 (1H, d, J 6.60 Hz, H-10), 5.55 (1H, m, H-12),2.71 (1H, m, H-9), 2.32 (1H, m, H-8), 1.21-2.08 (10H, m, H-2a, H-2b, H-3a, H-3b, H-4, H-5, H-6a, H-6b, H-7a, H-7b), 1.36 (3H, s, 1-CH_3), 0.98 (3H, d, J 5.76 Hz, 9-CH_3), 0.49 (3H, d, J 7.68 Hz, 5-CH_3) ppm; δ_C 140.37, 132.75, 128.66, 128.31, 103.10, 91.64, 81.91, 73.28, 52.23, 44.16, 38.28, 37.41, 34.93, 32.80, 26.47, 25.53, 20.63, 14.36; m/z (CI, CH_4) 407({[M(Cl^{37})+2CH_3]$^+$, 6}, 405 ({[M(Cl^{35})+2CH_3]$^+$,5), 379 ({[M(Cl^{37})-1]$^+$,97), 377 ([M(Cl^{35})-1]$^+$, 100), 355 (14), 333 (26), 182 (12). Anal. calc. for $C_{21}H_{27}O_2Cl$ C, 66.57; H, 7.18; found C, 66.42; H, 7.05.
40	9-anthryl  (10ß-isomer)	-	-	White solid. δ_H 9.00-9.05 (1H, m, Ar-H), 8.31-8.41 (2H, m, Ar-H), 7.05-8.04 (2H, m, Ar-H), 7.39-7.57 (4H, m, Ar-H), 7.23 (1H, d, J=7.51 Hz, H-10), 5.81 (1H, s, H-12), 3.10-3.23 (1H, m), 0.86-2.49 (11H, m), 1.39 (3H, s, H-14), 1.09 (3H, d, J=5.81 Hz, H-15), 0.57 (3H, d, J=7.72 Hz, H-16); δ_C 134.12, 131.70, 131.05, 130.88, 129.59, 129.19, 128.73, 128.47, 127.61, 126.05, 124.55, 124.51, 124.32, 123.71, 102.64, 91.22, 81.42, 72.62, 51.50, 44.18, 37.69, 36.87, 34.33, 33.02, 25.71, 25.09, 25.00, 19.94, 13.81.

Ex. No.	Y	R^1	R^2	Physical data
41	9-phenanthryl  (10ß-isomer)	-	-	White solid. M.p. 89-89.1°C; $[\alpha]_D^{20}$: -68.8° (c 0.016 $CHCl_3$); ν_{max} (film) 2922, 2874, 2362, 1498, 1450, 1376, 1246, 1220, 1110, 1040, 1010, 956, 930, 906, 886, 832, 794, 748, 726; δ_H: 8.68-8.81 (2H, m, Ar-H), 7.91-8.10 (3H, m, Ar-H), 7.57-7.72 (4H, m, Ar-H), 6.50 (1H, d, J=6.54 Hz, H-10), 5.75 (1H, s, H-12), 3.06-3.19 (1H, m), 2.37-2.48 (1H, m), 2.00-2.16 (3H, s), 1.73-1.84 (2H, m), 0.86-1.60 (5H, m), 1.41 (3H, s, H-14), 1.06 (3H, d, J=5.67 Hz, H-15), 0.39 (3H, d, J=7.61 Hz, H-16); δ_C: 135.21, 131.68, 130.14, 129.96, 129.59, 128.84, 126.66, 126.52, 126.04, 126.01, 123.84, 123.68, 123.19, 122.33, 102.47, 91.34, 81.42, 69.92, 51.45, 43.77, 37.71, 36.89, 34.27, 31.55, 25.79, 25.11, 24.95, 19.96, 13.22; m/z (CI, CH_4) 445 (M^++1, 22), 444 (100), 398 (40), 384 (16), 352 (16), 328 (44), 267 (6), 218 (84), 203 (48), 178 (60), 163 (44), 138 (70), 107 (62).
42	2-OCH_3 phenyl (10ß-isomer)	-	-	White solid. M.p. 61°C; $[\alpha]_D^{20}$:-14.4° (c 0.049 $CHCl_3$); ν_{max} (film) 2928, 2874, 1590, 1492, 1462, 1374, 1284, 1240, 1178, 1110, 1102, 1052, 1010, 944, 882, 854, 754; δ_H 6.83-7.50 (4H, m, Ar-H), 5.94 (1H, d, J=6.65, Hz, H-10), 5.58 (1H, s, H-12), 3.84 (3H, s, OCH_3), 2.86-2.99 (1H, m, H-9), 2.30-2.40 (1H, m), 1.19-2.11 (10H, m), 1.39 (3H, s, H-14), 1.01 (1H, d, J = 5.77 Hz, H-16), 0.43 (1H, d, J=7.64 Hz, H-15); δ_C 134.85, 127.00, 126.37, 120.02, 109.19, 90.86, 68.63, 55.19, 51.30, 43.39, 37.53, 36.72, 34.21, 29.87, 25.68, 24.97, 24.75, 19.83, 13.45; m/z (CI, CH_4) 375 (M^++1, 12%), 374 (M^+, 16), 342 (100), 329 (48), 311 (14), 284 (28), 182 (56), 148 (76), 137 (60), 121 (48): Anal.Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.07; found: C, 70.78; H, 8.28.

Ex. No.	Y	R^1	R^2	Physical data
43	2,4-$(OCH_3)_2$phenyl (10ß-isomer)	-	-	White snow-like crystal. M.p. 62°C; $[\alpha]_D^{26.5}$ - 64.21° (c. 0.0114 in $CHCl_3$); (Found C, 68.55; H, 8.14 $C_{33}H_{32}O_7$ requires C, 68.29; H, 7.97%); ν_{max} (Nujol): 2920, 1614, 1590, 1506, 1464, 1376, 1286, 1258, 1208, 1156, 1120, 1040, 1010, 946, 880, 832, 780, 726 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$) δ_H 7.33 (1H, d, J 8.40 Hz, H-6'), 6.47 (1H, dd, J 8.40, 2.40 Hz, H-5'), 6.42 (1H, d, J 2.40 Hz, H-3'), 5.84 (1H, d, J 6.60 Hz, H-10), 5.54 (1H, s, H-12), 3.80, 3.79 (6H, 2xs, 2xOMe), 2.84 (1H, m, H-9), 2.32 (1H, m, H-8), 1.20-2.10 (10H, m, H-2a, H-2b, H-3a, H-3b, H-4, H-5, H-6a, H-6b, H-7a, H-7b), 1.37 (3H, s, 1-CH_3), 1.00 (3H, d, J 5.70 Hz, 9-CH_3), 0.40(3H, d, J 7.50 Hz, 5-CH_3) ppm; m/z (CI, CH_4) 405 ([M+1]$^+$, 15), 359 ([-3CH_3]$^+$, 100), 317 (6), 275 (28), 221 (8), 154 (22). Anal.Calc. for $C_{33}H_{32}O_7$: C, 68.29; H, 7.97%; found C, 68.55; H, 8.14; C, 68.47; H, 8.37.
44	2,4,6-$(OCH_3)_3$ phenyl (10ß-isomer)	-	-	Colourless oil. $[\alpha]_D^{23}$+10.6° (c 0.016/ $CHCl_3$); ν_{max} (film) 2930, 1608, 1456, 1204, 1154, 1126, 1006, 954; δ_H: 6.16 (1H, d, J=8.09 Hz, H-10), 6.13 (2H, s, Ar-H), 5.52 (1H, s, H-12), 3.81 (3H, s, OMe), 3.78 (2x3H, s, OMe), 2.64-2.72 (1H, m), 2.29-2.38 (1H, m), 1.97-2.08 (2H, m), 1.68-1.84 (4H, m), 1.20-1.57 (3H, m), 1.40 (3H, s, H-14), 0.84-1.11 (1H, m), 1.00 (3H, d, J=5.73 Hz, H-15), 0.72 (3H, d, J=7.70 Hz, H-16); m/z (CI, CH_4) 435 (M^++1, 10), 417 (8), 389 (100), 371 (6), 347 (10), 329 (16), 221 (8): Anal.Calcd. for $C_{24}H_{34}O_8$; C, 66.34; H, 7.89; found: C 66.57; H, 8.04.

Ex. No.	Y	R^1	R^2	Physical data
45	2,4,6-$(CH_3)_3$, phenyl (10ß-isomer)	-	-	Colourless oil. $[\alpha]_D^{22}$+13.7 (c 0.019/$CHCl_3$); ν_{max} (film) 2938, 2874, 1452, 1376, 1208, 1106, 1076, 1008, 958, 942, 896, 880, 848, 780, 756, 724; δ_H: 6.81 (2H, s, Ar-H), 6.05 (1H, d, J=7.57 Hz, H-10), 5.55 (1H, s, H-12), 2.74-2.85 (1H, m), 2.48 (3H, s, Me), 2.26-2.40 (1H, m), 2.32 (3H, s, Me), 2.27 (3H, s, Me), 2.05-2.11 (2H, m), 1.64-1.90 (4H, m), 1.29-1.50 (3H, m), 1.41 (3H, s, H-14), 0.84-1.04 (1H, m), 1.03 (3H, d, J=5.91 Hz, H-15), 0.64 (3H, d, J=7.84 Hz, H-16); δ_C: 137.22, 135.56, 135.21, 133.52, 130.81, 128.37, 102.30, 90.71, 80.94, 71.82, 51.32, 43.92, 37.59, 36.79, 34.24, 30.44, 25.72, 25.04, 24.46, 22.28, 20.70, 20.63, 19.87, 13.22; m/z (CI, CH_4) 387 (M*+1, 6), 386 (8), 385 (10), 341 (100), 327 (8), 299 (8), 267 (14), 221 (10), 209 (4), 163 (8), 133 (8); Anal.Calcd. $C_{24}H_{34}O_4$: C, 74.58; H, 8.87; found: C, 74.49; H, 8.86.
46	2,4,5-$(CH_3)_3$, phenyl (10ß-isomer)	-	-	Colourless Oil. M.P. 141°C; $[\alpha]_D^{20}$:55.6° (c 0.068/$CHCl_3$); ν_{max} (film) 2922, 2874, 1502, 1452, 1374, 1278, 1220, 1202, 1180, 1120, 1100, 1056, 1040, 1000, 978, 954, 934, 896, 880, 820, 754; δ_H: 7.32 (1H, s, Ar-H), 6.99 (1H, s, Ar-H), 5.94 (1H, d, J=6.71 Hz, H-10), 5.67 (1H, s, H-12), 2.80-2.90 (1H, m), 2.38-2.48 (1H, m), 2.33 (2x3H, s, Me), 2.31 (3H, s, Me), 2.10-2.19 (2H, m), 1.70-2.00 (3H, m), 1.40-1.55 (4H, m), 1.47 (3H, s, H-14), 0.97-1.11 (1H, m), 1.11 (3H, d, J=5.75 Hz, H-15), 0.55 (3H, d, J=7.68 Hz, H-16); δ_C: 136.62, 134.02, 133.11, 131.04, 130.76, 127.09, 102.11, 91.04, 81.07, 70.00, 51.33, 43.49, 37.57, 36.73, 34.23, 29.89, 25.57, 25.01, 24.81, 19.89, 19.17, 18.73, 13.65; m/z (CI, CH_4) 387 (M*+1.10), 386 (M*, 44), 354 (60), 341 (84), 296 (6), 282 (18), 109 (20, 182 (28), 160 (100), 149 (56), 133 (38), 121 (30); Anal.Calcd. for $C_{24}H_{34}O_4$: C, 74.58; H, 8.87; found: C, 74.63, H, 8.73.

Ex. No.	Y	R^1	R^2	Physical data
47	4-COOH phenyl (10ß-isomer)	-	-	White solid. $[\alpha]_D^{20}$-61.2° (c 0.019/ $CHCl_3$); ν_{max} (film) 2954, 2878, 2670, 2546, 2252, 1688, 1612, 1578, 1512, 1452, 1424, 1376, 1314, 1286, 1222, 1208, 1178, 1116, 1074, 1056, 1040, 1012, 980, 968, 954, 944, 908, 882, 854, 824, 802, 766, 732; δ_H 8.09 (2H, d, J=8.34 Hz, Ar-H), 7.45 (2H, d, J=8.34 Hz, Ar-H), 5.82 (1H, d, J=6.63 Hz, H-10), 5.60 (1H, s, H-12), 2.76-2.83 (1H, m), 2.31-2.40 (1H, m), 1.23-2.10 (9H, m), 1.41 (3H, s, H-14), 0.87-1.02 (1H, m) 1.01 (3H, d, J=5.49 Hz, H-15), 0.51 (3H, d, J=7.62 Hz, H-16); δ_C 171.66, 147.41, 129.71, 127.33, 126.15, 102.29, 90.80, 81.07, 72.74, 51.35, 43.29, 37.42, 36.53, 34.04, 31.94, 29.05, 25.60, 24.67, 19.78, 13.42; m/z (CI, CH_4) 389 (M^++1,8), 329 (100), 283 (36), 267 (20), 219 (26), 177 (80), 129 (64). Anal. Calc. for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27; found: C, 67.77; H, 7.32.
48	4-Phenyl-piperazino (10α-isomer)	-	-	White solid. M.p. 149-150 °C; $[\alpha]_D^{22}$ + 16.7° (c 1.24 in $CHCl_3$); ν_{max} (film): 2924, 1600, 1504, 1450, 1378, 1238, 1206, 1158, 1042, 984, 926, 880, 758, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.34 (2H, m), 7.03 (2H, d, J = 8.0 Hz, H-2",H-5"), 6.92 (1H, t, J = 7.3 Hz, H-4"), 5.39 (1H, s, H-12), 4.18 (1H, d, J = 10.2 Hz), 3.29-3.21 (6H, m), 2.90 (2H, m), 2.70 (1H, m), 2.45 (1H, m), 2.13 (1H, m), 1.95 (1H, m), 1.75 (2H, m), 1.70-1.20 (8H, m), 1.20-1.00 (4H, m), .93 (3H, d, J = 7.1 Hz, 6-methyl) ppm; ^{13}C NMR (76 MHz, $CDCl_3$) δ_C 151.6, 128.9, 119.3, 116.0, 103.8, 91.6, 90.4, 80.3, 51.7, 49.5, 47.2, 45.8, 37.4, 36.3, 34.3, 28.5, 25.9, 24.8, 21.6, 20.3, 13.4 ppm; MS (CI, CH_4) m/e 429 (M^++1, 88). Anal. Calcd. for $C_{25}H_{32}N_2O_4$: C, 70.06, H, 8.47, N, 6.53; Found: C, 69.74, H, 8.38, N, 6.35.

Ex. No.	Y	R^1	R^2	Physical data
49	4-(2'-methoxyphenyl)-piperazino (10α-isomer)	-	-	White solid. M.p. 158-159 °C; $[\alpha]_D^{20}$ + 12.2° (c. 0.752 in $CHCl_3$); ν_{max} (film): 2936, 1594, 1500, 1448, 1376, 1240, 1180, 1118, 1058, 982, 926, 880, 828, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.10-6.80 (4H, m, Ar-H), 5.30 (1H, s, H-12), 4.07 (1H, d, J = 10.2 Hz, H-10), 3.85 (3H, s, -OMe), 3.30-2.95 (6H, m), 2.95-2.75 (2H, m), 2.61 (1H, m), 2.35 (1H, m), 2.00 (1H, m), 1.85 (1H, m), 1.70 (2H, m), 1.60-1.15 (9H, m), 1.15-0.90 (4H, m), 0.84 (3H, 7.2 Hz, 6-methyl) ppm; ^{13}C NMR (76 MHz, $CDCl_3$) δ_C 152.3, 141.8, 122.5, 120.9, 118.1, 111.2, 103.8, 91.6, 90.4, 80.4, 55.3, 51.8, 51.1, 45.9, 37.4, 36.4, 34.3, 28.5, 26.0, 24.8, 21.7, 21.7, 20.3, 13.4 ppm; MS (CI, CH_4) *m/e* 459 (M^++1, 55). Anal. Calcd. for $C_{28}H_{39}N_2O_5$: C, 68.10, H, 8.35, N, 6.11; Found: C, 67.74, H, 8.35, N, 5.83.
50	4-(4'-fluorophenyl)-piperazino (10β isomer)	-	-	White solid. M.p. 157-158 °C; $[\alpha]_D^{20}$ + 23.1° (c 0.743 in $CHCl_3$); ν_{max} (film): 2933, 2842, 1704, 1689, 1654, 1617, 1560, 1516, 1456, 1381, 1314, 1249, 1227, 1205, 1160, 1135, 1111, 1061, 1047, 1027, 985, 921, 883, 853, 822, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.00-6.80 (4H, m Ar-H), 5.29 (1H, s, H-12), 4.07 (1H, d, J = 10.2 Hz), 3.15-3.05 (6H, m), 2.83 (2H, m), 2.60 (1H, m), 2.35 (1H, m), 2.00 (1H, m), 1.90 (1H, m), 1.73 (2H, m), 1.70-1.10 (9H, m), 1.10-0.90 (4H, m), 0.83 (3H, d, J = 7.1 Hz, 6-methyl) ppm; ^{13}C NMR (76 MHz, $CDCl_3$) δ_C 156.8 (d, $^1J_{C-F}$ = 238 Hz), 148.2 (d, $^4J_{C-F}$ = 1.96 Hz), 117.6 (d, $^3J_{C-F}$ = 7.55 Hz), 115.2 (d, $^2J_{C-F}$ = 21.9 Hz), 103.7, 91.5, 90.3, 80.2, 51.6, 50.4, 47.1, 45.7, 37.3, 36.2, 34.2, 28.4, 25.9, 24.7, 21.5, 20.2, 13.3 ppm; MS (CI, CH_4) *m/e* 447 (M^++1, 82). Anal. Calcd. for $C_{28}H_{35}N_2O_4F$: C, 67.24, H, 7.90, N, 6.27; Found: C, 67.28, H, 8.01, N, 5.95.

Ex. No.	Y	R^1	R^2	Physical data
51	4-(2'-pyridyl)-piperazino (10α-isomer)	-	-	White solid. M.p. 146-147 °C; $[\alpha]_D^{20}$ + 16.4° c 1.34 in $CHCl_3$); ν_{max} (film) 2926, 2872, 1596, 1564, 1482, 1346, 1378, 1312, 1248, 1208, 1160, 1132, 1056, 1026, 980, 926, 880, 850, 828, 744, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 8.17 (1H, dd, J = 1.3, 5.0 Hz, H-6"), 7.44 (1H, td, J = 1.8, 3.4 Hz, H-4"), 6.64-6.55 (2H, m, H-3" & H-5"), 5.27 (1H, s, H-12), 4.07 (1H, d, J = 10.3 Hz, H-10), 3.52-3.48 (4H, m, H-3' & H-5'), 3.10-3.05 (2H, m), 2.79 -2.74 (2H, m), 2.76 (1H, m), 2.32 (1H, m), 2.02-1.80 (2H, m), 1.70-1.65 (2H, m), 1.50-1.20 (8H, m), 1.10-0.90 (4H, m), 0.83 (3H, d, J = 7.2 Hz, 6-methyl) ppm; ^{13}C NMR (76 MHz, $CDCl_3$) δ_C 153.6, 147.8, 137.2, 112.8, 107.0, 103.8, 91.6, 90.6, 80.3, 51.7, 47.1, 45.8, 45.5, 37.3, 36.3, 34.3, 28.5, 25.9, 24.7, 21.6, 20.3, 13.4 ppm; MS (CI, NH_3) m/e 430 (M^++1, 100); Anal. Calcd. for $C_{24}H_{35}N_3O_4$: C, 67.11, H, 8.21, N, 9.78; Found: C, 67.01, H, 8.22, N, 9.55.

Ex. No.	Y	R^1	R^2	Physical data
52	4-(3'-trifluoromethyl-phenyl)-piperazino (10α-isomer)			White solid, M.p. 126-127 °C; $[\alpha]_D^{20}$ + 21.0° (c, 0.543 in $CHCl_3$); ν_{max} (film): 2928, 2874, 1612, 1588, 1496, 1450, 1412, 1378, 1356, 1320, 1266, 1242, 1208, 1164, 1122, 1100, 1054, 986, 948, 926, 880, 860, 828, 788, 732, 696, 640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.33 (1H, m, H-5''), 7.10-7.02 (3H, m, Ar-H), 5.30 (1H, s, H-12), 4.09 (1H, d, J = 10.2 Hz, H-10), 3.40-3.05 (6H, m), 2.84 (2H, m), 2.65 (1H, m), 2.35 (1H, m), 2.20 (1H, m), 1.85 (1H, m), 1.80-1.60 (2H, m), 1.50-1.15 (10H, m), 0.90 (4H, m), 0.84 (3H, d, J = 7.2 Hz); ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 151.7, 129.6, 118.7, 115.4, 111.9, 103.9, 91.6, 90.5, 80.3, 51.7, 49.0, 47.0, 45.8, 37.4, 36.3, 34.3, 28.5, 25.9, 24.8, 21.6, 20.3, 13.4 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ_F 63.9 ppm; MS (CI, CH_4) m/e 497 (M^++1, 58). Anal. Calcd. for $C_{28}H_{35}N_2OF_3$: C, 62.89, H, 7.10, N, 5.64; Found: C, 62.82, H, 7.27, N, 5.58.

Ex. No.	Y	R^1	R^2	Physical Data
53	4-Fluorophenyl (1OS-isomer)	-	-	White solid. M.P. 133.6-134.8 °C, $[\alpha]_D^{24}$ -35.66° (c 0.83, $CHCl_3$); δ_F: -118.00; IR (neat) ν_{max} : 2952, 2873, 1604, 1510, 1452, 1376, 1222, 1110, 1040, 1010, 944, 906, 882, 838, 782; δ_H: 7.29-7.24 (2H, m, Ph), 7.04-6.97 (2H, m, Ph), 5.70 (1H, d, H-10, J=6.70 Hz), 5.55 (1H, s, H-12), 2.77-2.65 (1H, m), 2.39-2.28 (1H, m), 2.10-1.97 (2H, m), 1.90-1.82 (1H, m), 1.78-1.64 (2H, m), 1.49-1.42 (1H, m), 0.99 (3H, s), 0.88 (3H, s); δ_C: 162.10 (d, Ph, J_{CF}=246.0 Hz), 137.42 (d, Ph, J_{CF}=3.09 Hz), 128.30 (d, Ph, J_{CF}=7.84 Hz), 115.16 (d, Ph, J_{CF}=21.27 Hz), 102.92, 91.55, 81.75, 73.15, 52.09, 44.05, 38.14, 37.30, 34.82, 32.78, 26.35, 25.57, 25.42, 20.52, 14.29; MS (CI positive, NH_3) m/z: 382 (MNH_4^+, 2 x ^{13}C, 4%), 381 (MNH_4^+, ^{13}C, 25%), 380 (MNH_4^+, base peak), 363 (MH^+, 6%); Anal Calcd. for $C_{19}H_{23}O_4F$ C 69.59, H 7.51; found C 69.51, H 7.62.

Ex. No.	Y	R^1	R^2	Physical data
54	1-(2-pyrimidyl)-piperazino (10ß-isomer)	-	-	White solid. M.p. 147.1-147.5 °C; $[\alpha]_D^{20}$: +14.3° (c = 0.86, $CHCl_3$); IR (KBr) ν_{max} 2988, 2970, 2948, 2918, 2870, 2854, 1588, 1546, 1502, 1452, 1438, 1430, 1396, 1376, 1308, 1268, 1186, 1160, 1132, 1114, 1102, 1060, 1044, 1022, 980, 940, 926, 880, 852, 826, 798, 742, 694, 640; δ_H: 8.27 (2H, d, o-Ph, J=4.8 Hz), 6.43 (1H, t, p-Ph, J=4.8 Hz), 5.27 (1H, s, H-12), 4.05 (1H, d, H-10, J=10.2 Hz), 3.87-3.72 (4H, m, $2xNCH_2$), 3.08-3.01 (2H, m), 2.75-2.59 (4H, $2xNCH_2$), 2.38-2.27 (1H, m), 2.02-1.37 (8H, m), 1.34 (3H, s, 3-Me), 1.33-1.17 (1H, m), 0.94 (3H, d, 6-Me, J=6.1 Hz), 0.85 (3H, d, 9-Me, J=7.16 Hz); δ_C: 162.39, 158.31, 110.17, 104.56, 92.34, 91.49, 80.99, 52.44, 47.95, 46.56, 44.76, 38.07, 37.02, 34.99, 29.20, 26.66, 25.44, 22.34, 20.97, 14.22; MS (CI, CH_4) m/z: 432 (MH^+, ^{13}C, 5%), 431 (MH^+, 33%); Anal. calcd for $C_{23}H_{34}N_4O_4$: C 64.16, H 7.96, N 13.01; found C 64.09, H 8.07, N 12.86.
55	1-(4-Chlorophenyl)-piperazino 10α-isomer	-	-	White solid. M.p. 140.7-142.8 °C; $[\alpha]_D^{20}$: +9.41° (c = 1.01, $CHCl_3$); IR (KBr) ν_{max} : 2976, 2952, 2934, 2894, 2872, 2842, 1596, 1502, 1454, 1378, 1350, 1316, 1286, 1248, 1206, 1184, 1160, 1136, 1108, 1060, 1046, 1026, 956, 982, 882, 852, 816, 698, 666, 518; δ_H: 7.20 (2H, d, Ph, J=9.0 Hz), 6.85 (2H, d, Ph, J=9.02 Hz), 5.30 (1H, s, H-12), 4.09 (1H, d, H-10, J=10.23 Hz), 3.20-3.07 (8H, m, 4 x NCH_2), 2.86-1.20 (15H, m), 0.96 (3H, d, 6-Me, J=6.09 Hz), 0.84 (3H, d, 9-Me, J=7.18 Hz); δ_C: 150.93, 129.49, 124.75, 117.83, 104.57, 92.29, 91.11, 81.02, 52.39, 50.18, 47.74, 46.51, 38.08, 36.99, 34.97, 29.21, 26.65, 25.45, 22.33, 20.97, 14.14; MS (CI positive, CH_4) m/z: 465 (MH^+, ^{37}Cl, 2%), 464 (MH^+, ^{13}C, 0.4%), 463 (MH^+, 6%); Anal. Calcd for $C_{25}H_{35}N_2O_4Cl$: C 64.85, H 7.62, N 6.05; found: C 64.68, H 7.66, N 5.89.

Ex. No.	Y	R^1	R^2	Physical data
56	1-(3-Chlorophenyl-piperazino 10α-isomer	-	-	White solid. M.p. 137.3-137.8 °C; $[\alpha]_D^{20}$: +12.13° (c = 0.89, $CHCl_3$); IR (KBr) ν_{max} 2976, 2948, 2922, 2876, 2864, 2848, 2826, 1598, 1566, 1486, 1452, 1430, 1412, 1378, 1360, 1328, 1312, 1284, 1274, 1264, 1244, 1206, 1184, 1158, 1136, 1116, 1102, 1086, 1042, 1028, 988, 942, 928, 880, 854, 832, 782, 774, 680; δ_H: 7.18-7.12 (1H, m, Ph), 6.88-6.77 (3H, m, Ph), 5.30 (1H, s, H-12), 4.08 (1H, d, H-10, J=10.21 Hz), 3.24-3.12 (6H, m, 3 x NCH_2), 2.84-2.78 (2H, m, NCH_2), 2.66-2.59 (1H, m), 2.41-2.30 (1H, m), 2.05-1.20 (13H, m), 0.96 (3H, d, 6-Me, J=6.06 Hz), 0.84 (3H, d, 9-Me, J=7.17 Hz); δ_C: 153.36, 135.54, 130.59, 119.58, 116.33, 114.58, 104.63, 92.34, 91.18, 81.05, 52.44, 49.75, 47.76, 46.55, 38.11, 37.02, 35.00, 29.25, 26.67, 25.48, 22.37, 20.99, 14.16; MS (ES) m/z: 465 (MH^+, ^{13}C, 10%), 464 (MH^+, ^{13}C, 9%), 463 (MH^+, 100%); Anal. Calcd for $C_{25}H_{35}N_2O_4Cl$: C 64.85, H 7.62, N 6.05, found: C 64.91, 7.73, N 6.00.
57	1-(2-Chlorophenyl)-piperazino	-	-	White solid. M. p. 72-75 °C, $[\alpha]_D^{20}$ -5.15° (c 1.01, $CHCl_3$); IR (neat) ν_{max} 3062, 2926, 2870, 2360, 1588, 1480, 1450, 1376, 1232, 1206, 1124, 1040, 984, 926, 880, 828, 762, 668; δ_H: 7.37-6.92 (4H, m, Ph), 5.32 (1H, s, H-12), 4.09 (1H, d, H-10, J=10.21 Hz), 3.23-3.05 (8H, m, 4 x NCH_2), 2.67-2.60 (1H, m, H-9), 2.41 (1H, m), 2.37-1.20 (13H, m), 0.96 (3H, d, 6-Me, J=6.14 Hz), 0.85 (3H, d, 9-Me, J=7.19 Hz); δ_C: 150.37, 131.31, 129.50, 128.11, 124.00, 120.99, 104.62, 92.40, 91.29, 81.07, 52.49, 52.38, 46.61, 38.09, 37.07, 35.02, 29.26, 26.72, 25.47, 22.39, 21.00, 14.21; MS (ES positive) m/z: 465 (MH^+, ^{37}Cl, 20%), 464 (MH^+, ^{13}C, 19%), 463 (MH^+, 100%); Anal. Calcd for $C_{25}H_{35}N_2O_4Cl$: C 64.85, H 7.62, N 6.05; found: C 64.92, H 7.67, N 5.77.

Ex. No.	Y	R^1	R^2	Physical data
58	1-(4-Methoxyphenyl)-piperazino	-	-	White solid. M.p. 147.6-148.4 °C; $[\alpha]_D^{20}$: +9.07° (c 1.08, $CHCl_3$); IR (KBr) ν_{max} 2958, 2924, 2846, 2810, 1512, 1464, 1448, 1420, 1378, 1350, 1326, 1310, 1292, 1264, 1248, 1206, 1182, 1160, 1134, 1108, 1086, 1060, 1038, 1026, 1010, 984, 942, 926, 880, 852, 824, 814, 800; δ_H: 6.93-6.81 (4H, m, Ph), 5.30 (1H, s, H-12), 4.08 (1H, d, H-10, J=10.20 Hz), 3.77 (3H, s, OMe), 3.20-3.04 (6H, m, 3 x NCH_2), 2.86-2.80 (2H, m, NCH_2), 2.66-2.59 (1H, m), 2.41-2.31 (1H, m), 2.05-1.21 (13H, m), 0.96 (3H, d, 6-Me, J=6.08 Hz), 0.84 (3H, d, 9-Me, J=7.16 Hz); δ_C: 154.22, 146.81, 118.81, 115.00, 104.53, 92.27, 91.08, 81.03, 56.22, 52.40, 51.70, 47.93, 46.54, 38.07, 37.00, 34.98, 29.22, 26.64, 25.46, 22.34, 20.98, 14.12; MS (ES positive) m/z: 459 (MH^+, 100%), 458 (M^+, 58%) Anal. Calcd for $C_{26}H_{38}N_2O_5$: C 68.10, H 8.35, N 6.11; found: C 68.16, H 8.42, N 5.97.
59	1-(ortho-Tolyl)-piperazino 10α-isomer	-	-	White solid, m.p. 141.6-142.8°C; $[\alpha]_D^{20}$ +12.55° (c 1.02, $CHCl_3$); IR (neat) ν_{max} 3026, 3021, 2926, 2872, 2360, 1598, 1492, 1448, 1376, 1328, 1306, 1258, 1226, 1206, 1180, 1156, 1132, 1118, 1056, 1040, 1026, 982, 958, 926, 880, 850, 828, 762, 722, 668; δ_H: 7.19-7.14 (2H, m, Ph), 7.07-6.94 (2H, m, Ph), 5.33 (1H, s, H-12), 4.10 (1H, d, H-10, J=10.17 Hz), 3.19-3.14 (2H, m, NCH_2), 2.97-2.79 (6H, m, 3 x NCH_2), 2.71-2.59 (1H, m, H-9), 2.37 (1H, m), 2.32 (3H, s, Ph<u>Me</u>), 2.07-2.00 (1H, m), 1.71-1.17 (11H, m), 0.97 (3H, d, 6-Me, J=6.1 Hz), 0.87(3H,d,9-Me,J=7.2Hz); δ_C: 174.96, 152.60, 133.43, 131.66, 127.07, 123.47, 119.54, 104.61, 92.45, 91.35, 81.08, 52.84, 52.48, 46.59, 38.07, 37.05, 35.00, 29.25, 26.75, 25.55, 22.38, 20.99, 18.64, 14.22; MS (CI CH_4) m/z: 444 (MH^+, ^{13}C, 5.1%), 443 (MH^+, 18%), 442 (M^+, 7.6%); Anal. Calcd for $C_{26}H_{38}N_2O_4$: C 70.56, H 8.65, N 6.33; found C 70.43, H 8.54, N 6.28.

Ex. No.	Y	R^1	R^2	Physical data
60	4-Benzylpiperidino 10α-isomer	-	-	White solid. M.p. 137.6-138.9 °C; $[\alpha]_D^{20}$: +10.82° (c 0.98, $CHCl_3$); IR (neat) ν_{max} : 2924, 2870, 1452, 1376, 1206, 1132, 1098, 1056, 970, 926, 880, 828, 746, 700; δ_H: 7.28-7.24 (2H, m, Ph), 7.19-7.12 (3H, m, Ph), 5.25 (1H, s, H-12), 4.00 (1H, d, H-10, J=10.16 Hz), 3.00-2.86 (2H, m), 2.69-2.27 (6H, m), 2.02-1.41 (10H, m), 1.38 (3H, s, 3-Me), 1.33-1.12 (4H, m), 1.09-0.97 (1H, m), 0.93 (3H, d, 6-Me, J=6.12 Hz), 0.78 (3H, d, 9-Me, J=7.18 Hz); δ_C: 141.60 (Ph), 129.75 (Ph), 128.73 (Ph), 126.28 (Ph), 104.44, 92.40, 91.75, 81.06, 52.46, 46.64, 44.16, 44.03, 38.85, 38.02, 37.02, 34.99, 33.49, 33.18, 29.36, 26.72, 25.41, 22.32, 20.97, 14.20; MS (CI positive, NH_3) m/z: 444 (MH^+, 2 x ^{13}C, 2%), 443 (MH^+, ^{13}C, 12%), 442 (MH^+, 38%), 441 (M^+, 1%); Anal Calcd. For $C_{27}H_{39}NO_4$: C 73.44, H 8.90, N 3.17; found C 73.25, H 8.85, N 3.14.

Ex. No.	Y	R^1	R^2	Physical data
61	6-Methoxynaphthyl 10α- and 10ß-isomers	-	-	δ_H: 7.73-7.70 (3H, m, Ph), 7.59-7.55 (1H, m, Ph), 7.13-7.10 (2H, m, Ph), 4.50 (1H, d, H-10, J=10.64 Hz), 3.91 (3H, s, OMe), 2.72-2.65 (1H, m), 2.49-2.43 (1H, m), 2.10-2.02 (1H, m), 1.96-1.87 (1H, m), 1.81-1.74 (1H, m), 1.68-1.53 (4H, m), 1.46 (3H, s, 3-Me), 1.42-1.24 (3H, m), 1.13-1.05 (1H, m), 0.99 (3H, d, 6-Me, J=6.15 Hz), 0.55 (3H, d, 9-Me, J=7.19 Hz); δ_C: 158.18, 136.70, 135.07, 130.13, 129.28, 127.65, 127.01, 126.46, 119.24, 106.32, 104.92, 92.76, 81.36, 79.15, 55.93, 52.70, 46.78, 38.12, 37.05, 34.93, 34.55, 26.75, 25.51, 22.20, 21.01, 14.80; MS (ES positive) m/z: 424 (MH^+, 4%). δ_H: 7.74-7.67 (3H, m, Ph), 7.39-7.35 (1H, m, Ph), 7.14-7.11 (2H, m, Ph), 5.86 (1H, d, H-10, J=3.72 Hz), 5.54 (1H, s, H-12), 3.91 (3H, s, OMe), 2.86-2.78 (1H, m), 2.40-2.30 (1H, m), 2.09-1.58 (5H, m), 1.51-1.23 (7H, m), 0.99 (3H, d, 6-Me, J=5.58 Hz), 0.94-0.88 (1H, m), 0.52 (3H, d, 9-Me, J=7.65 Hz); $ä_C$: 157.97, 137.12, 134.08, 130.11, 129.39, 126.83, 126.19, 124.98, 119.23, 106.29, 103.09, 91.72, 81.99, 73.86, 55.94, 52.29, 44.28, 38.29, 37.45, 34.97, 32.96, 26.51, 25.70, 25.57, 20.67, 14.52; MS (CI positive, CH_4) m/z: 426 (MH^+, ^{13}C, 2%), 425 (MH^+, 8%), 424 (M^+, 7%).

Example 62

The parasiticidal activity of compounds of the invention was investigated by means of the following tests.

Abbreviations used in the examples:

CO_2 = carbon dioxide

DMSO = dimethylsulphoxide

ED = dermal cell line of a horse

EDTA = ethylenediaminetetraacetic acid

FCS = fetal calf serum

RPMI = growth medium for cell cultures

rpm = revolutions per minute

VERO = kidney cell line of the African green monkey

(a) Screening of compounds against Neospora Caninum cell cultures in vitro.

Screening was conducted in 96-well plates (Falcon 3872). A monolayer of host cells (VERO or ED) were placed on a cell culture plate. Non-infected monolayers of cells were cultured in two 50 ml tissue culture bottles (50 cm^3 cell culture area). The cell layer was detached with trypsin-EDTA (5 ml. Gibco 45300-019) in a CO_2-culture cupboard at 37°C. After 10 minutes, most of the cells were detached. The cells were transferred with a 5 ml pipette into a 50 ml centrifuge tube (Greiner, B769331) containing about 1 ml warmed fetal calf serum. After centrifugation for 5 minutes at 1500 rpm (Varifuge 3.0, Heraeus), the

liquid was removed and the cell pellet suspended in RPMI medium (100 ml, 95% RPMI 1640, 2% FCS, 1% L-glutamine, 1% sodium hydrogen carbonate, 1% penicillin/streptomycin). The cell suspension was pipetted into six 96-well plates at 150 µl per well. The coated cell culture plates were placed in an incubation cupboard at 37°C under 5% CO_2 for 24 hours. The cells were then infected with Neospora caninum tachyzoites at a concentration of 48,000 tachyzoites per well. This was followed by incubation at 37°C under 5% CO_2 for 24 hours.

The test compounds (0.5 - 1.5 mg) were weighed into 1.5 ml eppendorf vessels and dissolved in 1 ml dimethyl sulphoxide, corresponding to a dilution of about 1 x 10^{-3} g ml^{-1}. The medium used for further dilution consisted of 87% RPMI 1640, 10% FCS, 1% L-glutamine, 1% sodium hydrogen carbonate, 1% penicillin/streptomycin. In the first screening, concentrations of 10^{-5}, 10^{-6} and 10^{-7} g ml^{-1} were used. The diluted preparations were then transferred to the cell culture plates at a volume of 150 µl per well after 24 hour infection with Neospora caninum. For the first row, untreated medium was used; this row contained infected and uninfected cells as controls. The cell plate was incubated at 37°C under 5% CO_2 for 5 days. Microscopic evaluation was conducted 4 days after treatment and 5 days after infection at a magnification of 25 x 10 in an inverse microscope according to the following evaluation scheme.

Evaluation	Observable effect
0 = no effect	monolayer completely destroyed
1 = weak effect	monolayer partly destroyed, parasite clumps can be seen
2 = full effect	monolayer intact, no tachyzoites observable
T = cytotoxic	cells are dead, lysed

The results are set out in Table II below:-

Table II

Example No.	Dose (g/ml)			
	10^{-5}	10^{-6}	10^{-7}	10^{-8}
2	1	1	0	-
15	T/1	1	1	0
18	2	1	0	-
19	T	0	-	-
20	T/1	1	1	0
21	2	0	-	-
23	T/2	0	-	-
24	1	0	-	-
25	T/1	1	1	0
30	1	0	-	-
31	2	1	0	-
32	2	0	-	-
Artemisinin	0	-	-	-

(b) Screening of Compounds again Eimeria Tenella cell cultures in vitro

Cells from kidneys of 19 day old chicks are cultured as monolayers in 96-well plates (Falcon 3872) in a medium of Hanks lactalbumine hydrolysate, 5% fetal calf serum, 1% glutamine and 1% non-essential amino acids. After two days at 42°C under 5% CO_2, the culture was infected with excised sporozoites of Eimeria tenella at about 30.00 per well. Test compounds were dissolved in DMSO and diluted with culture medium to a maximum end concentration of $10\mu g\ ml^{-1}$. The dilution steps were 1:10. On day 5 post infection, the cultures were evaluated under a microscope at 100-fold magnification and the condition of the host cells and the amount of intact schizonts

and free merozoites was determined. Effectiveness was rated as follows:

Evaluation	Observable effect
3 = very active	no intact parasites/well
2 = active	1-6 parasites per well
1 = weakly active	up to 1 intact schizont/optical field of vision
0 = inactive	> 1 intact schizont/optical field of vision
T = cytotoxic	host cells are dead

The results are set out in Table III below:-

Table III

Example No.	Dose (g/ml)			
	10^{-5}	10^{-6}	10^{-7}	10^{-8}
2	2	2	1	0
15	2	2	1	0
18	T	T	1	0
19	T	T	1	0
20	T	T/2	0	-
21	T/2	0	-	-
23	T	T/2	0	-
24	2	1	0	-
25	2	1	1	0
30	T	2	0	-
31	T	1	0	-
32	T	2	0	-
Artemisinin	2	1	0	-

(c) *In Vitro* Screening against *Plasmodium Falciparum*

Two parasite strains - W2 resistant to chloroquine, and D6 sensitive to chloroquine but resistant to mefloquine were used. In Table IV below, the best compounds should show no cross resistance between the two strains.

The assay relies on incorporation of radiolabelled

hypoxanthine by the parasite and inhibition of incorporation is attributed to activity of known or candidate antimalarial drugs. For each assay, proven antimalarials such as chloroquine, mefloquine, quinine, artemisinin and pyrimethamine were used as controls. The incubation period was 66 hours, and the starting parasitemia was 0.2% with 1% hematocrit. The medium was an RPMI-1640 culture with no folate or p-aminobenzoic acid. Albumax rather than 10% normal heat inactivated human plasma was used as, with Albumax, less protein binding is observed, and compounds elicit slightly higher activities in this model. If a compound was submitted with no prior knowledge of activity, it was dissolved directly in dimethyl sulphoxide (DMSO), and diluted 400 fold with complete culture medium. The unknown compound was started at a maximum concentration of 50,000 ng ml^{-1} and sequentially diluted 2-fold for 11 times to give a concentration range of 1048 fold. These dilutions were performed automatically by a Biomek 1000 Liquid Handling System in 96-well microtiter plates. The diluted drugs were then transferred to test plates, 200 μl of parasitized erythrocytes were added, and incubated at 37°C in a controlled environment of 5% CO_2, 5% O_2 and 90% N_2. After 42 hours, 25 μl of ^{3}H-hypoxanthine was added, and the plates incubated for an additional 24 hours. After 66 hours, the plates were frozen at -70°C to lyse the red cells, and then thawed and harvested onto glass fiber filter mats in a 96-well harvester. The filter mats were then counted in a scintillation counter. For each drug, the concentration response profile was determined and 50%, 90% and 10% inhibitory concentrations (IC_{50}, IC_{90} and IC_{10}) were determined by a non-linear logistic dose response analysis program.

A prescreen format can be used wherein a 3-dilution assay may be used to determine activity at high medium or low concentrations. The concentrations were selected as 50,000, 500 and 50 ng ml^{-1}. These were performed in duplicate on a 96-well format plate with 14 test compounds and one known (standard) compound per plate. The system was automated with a Biomek diluter for mixing and diluting the drugs, and adding drugs and parasites to a test plate.

In the prescreen format, if the ANALYSIS FIELD (AF) has a "<", then the compound was "very active" and the IC values are most likely to be below the last dilution value (in nanograms/ml), which is listed next to AF. In most cases, these compounds were run again at lower starting concentration to determine the true IC value. If the AF has a ">", then the IC value is greater than the prescreen dilution value; thus "AF>250" means that the IC value is greater than 250 ng ml^{-1} and no further screening is carried out. In such cases, values of 0.00 are entered for IC values.

The results are set out in Table IV below:-

Table IV

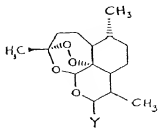
Example No.	In vitro activity: IC_{50}; IC_{90}; (IC_{10}) ng/ml	
	W2 Strain (Chloroquine resistant)	D6 Strain (Chloroquine sensitive)
1A (10α-isomer)	0.69; 0.97	0.64; 1.24
1B (10ß-isomer)	0.69; 0.98	0.74; 1.36
2	0.31; 0.52; (0.19)	0.73; 0.99; (0.53)
4	0.84; 1.74; (0.40)	1.05; 2.10; (0.52)
12	0.78; 1.32, (0.47)	0.77; 1.70; (0.35)
15	0.66; 0.84; (0.52)	0.61; 0.78; (0.48)
16	0.64; 0.84; (0.49)	0.61; 0.78; (0.48)
18	0.23; 0.33; (0.17)	0.28; 0.82; (0.09)
19	0.33; 0.43; (0.25)	0.39; 0.80; (0.19)
20	5.81; 12.77; (2.64)	9.40; 12.93; (6.84)
21	0.00; 0.00 250AF<0	1.77; 3.96; (0.79)
23	0.00; 0.00; AF>250	0.00; 0.00; AF>250
24	0.77; 1.30; (0.46)	1.17; 2.10; (0.65)
25	0.11; 0.17; (0.07)	0.09; 0.35; (0.02)
26	0.00; 0.00 AF<4	9.05; 16.24; (5.05)
30	0.00; 0.00; 250AF<0	11.20; 18.61; (6.74)
31	0.29; 0.68; (0.12)	1.35; 2.42; (0.75)
32	0.45; 0.92; (0.22)	2.45; 3.97; (1.51)
36	0.26; 0.61; (0.11)	0.38; 0.77; (0.19)
38	1.23; 2.76 (0.55)	0.90; 3.69; (0.22)

Table IV (cont)

Example No.	In vitro activity: IC_{50}; IC_{90}; (IC_{50}) ng/ml	
	W2 Strain (Chloroquine resistant)	D6 Strain(Chloroquine sensitive)
41	0.73; 1.7; (0.30)	1.53; 2.04; (1.16)
44	0.3318; 0.8168; (0.13)	0.69; 1.67; (0.29)

CLAIMS

1. A compound of the general formula I



(I)

or a salt thereof,

in which

Y represents a halogen atom, an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclylalkyl group or a group $-NR^1R^2$; where

R^1 represents a hydrogen atom or an optionally substituted alkyl, alkenyl or alkynyl group;

R^2 represents an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl group; or

R^1 and R^2 together with the interjacent nitrogen atom represent an optionally substituted heterocyclic group or an amino group derived from an optionally substituted amino acid ester;

for use in the treatment and/or prophylaxis of a disease caused by infection with a parasite other than an organism of the genus Plasmodium.

2. A compound according to claim 1 in which Y represents a halogen atom.

3. A compound according to claim 1 or claim 2 in which Y represents a fluorine or bromine atom.

4. A compound according to claim 1 in which Y represents a C_{3-8} cycloalkyl group, a C_{6-18} aryl group, a 5- to 10-membered C-linked heteroaryl group or a 5- to 10-membered heterocyclyl-C_{1-6} alkyl group, each group being optionally substituted by one or more substituents selected from the group consisting of halogen atoms, hydroxyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, carboxyl, C_{6-10} aryl, 5 to 10-membered heterocyclic and C_{1-4} alkyl- or phenyl-substituted 5- to 10-membered heterocyclic groups.

5. A compound according to claim 4 in which Y represents a C_{6-18} aryl group optionally substituted by one or more substituents selected from the group consisting of halogen atoms, hydroxyl, C_{1-4} alkyl, C_{2-4} alkenyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, C_{1-4} haloalkoxy, amino, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino and carboxyl groups.

6. A compound according to claim 4 or claim 5 in which Y represents a phenyl, naphthyl, anthryl or phenanthryl group, each group being optionally substituted by one or more substituents selected from the group consisting of halogen atoms and hydroxyl, methyl, vinyl, C_{1-4} alkoxy and carboxyl groups.

7. A compound according to any one of claims 4 to 6 in which Y represents a phenyl, fluorophenyl chlorophenyl, bromophenyl, trimethylphenyl, vinylphenyl, methoxyphenyl,

dimethoxyphenyl, trimethoxyphenyl, carboxylphenyl, naphthyl, hydroxynaphthyl, methoxynaphthyl, anthryl or phenanthryl group.

8. A compound according to any one of claims 4 to 7 in which Y represents a phenyl or trimethoxyphenyl group.

9. A compound according to claim 1 in which Y represents a group $-NR^1R^2$ where R^1 represents a hydrogen atom or a C_{1-6} alkyl group and R^2 represents a C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{6-10} aryl or C_{7-16} aralkyl group, or R^1 and R^2 together with the interjacent nitrogen atom represent a 5- to 10-membered heterocyclic group or an amino group derived from a C_{1-6} alkyl ester of an amino acid, each group being optionally substituted by one or more substituents selected from the group consisting of halogen atoms, C_{1-6} alkyl, C_{1-4} haloalkyl, C_{1-6} alkoxycarbonyl, phenyl, halophenyl, C_{1-4} alkylphenyl, C_{1-4} haloalkylphenyl, C_{1-4} alkoxyphenyl, benzyl, pyridyl and pyrimidinyl groups.

10. A compound according to claim 9 in which Y represents a group $-NR^1R^2$ where R^1 represents a hydrogen atom or a C_{1-4} alkyl group and R^2 represents a C_{1-6} alkyl, C_{3-6} cycloalkyl, phenyl or benzyl group, or R^1 and R^2 together with the interjacent nitrogen atom represent a 6- to 10-membered heterocyclic group or an amino group derived from a C_{1-4} alkyl ester of an amino acid, each group being optionally substituted by one or more substituents selected from the group consisting of halogen atoms, C_{1-4} haloalkyl, C_{1-4} alkoxycarbonyl, phenyl, halophenyl, C_{1-4} alkylphenyl, C_{1-4} haloalkylphenyl, C_{1-4} alkoxyphenyl, benzyl, pyridyl and pyrimidinyl groups.

11. A compound according to claim 9 or claim 10 in which Y represents a propylamino, cyclopentylamino, cyclohexylamino, phenylamino, fluorophenylamino, chlorophenylamino, bromophenylamino, iodophenylamino, methoxycarbonylphenylamino, biphenylamino, benzylamino, fluorobenzylamino, bis(trifluoromethyl)benzylamino, phenylethylamino, phenyl-methoxycarbonylmethylamino, diethylamino, morpholinyl, thiomorpholinyl, morpholinosulphonyl, indolinyl, tetrahydroisoquinolinyl, phenylpiperazinyl, fluorophenylpiperazinyl, chlorophenylpiperazinyl, methylphenylpiperazinyl, trifluoromethylphenylpiperazinyl, methoxyphenylpiperazinyl, benzylpiperazinyl, pyridylpiperazinyl and pyrimidinylpiperazinyl group.

12. A compound according to any one of claims 9 to 11 in which Y represents a propylamino, phenylamino, bromophenylamino, iodophenylamino, biphenylamino, benzylamino, bis(trifluoromethyl)benzylamino, phenylethylamino, phenyl-methoxycarbonylmethylamino or morpholinyl group.

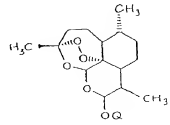
13. A compound according to any one of the preceding claims in which the parasite is an organism of the genus Neospora or the genus Eimeria.

14. Use of a compound of the general formula I as defined in any one of claims 1 to 12 for the manufacture of a medicament for the treatment and/or prophylaxis of a disease caused by infection with a parasite other than an organism of the genus Plasmodium.

15. Use according to claim 14 in which the parasite is an organism of the genus Neospora or the genus Eimeria.

16. A compound of the general formula I as defined in any one of claims 1 to 12, with the proviso that, when Y is a group $-NR^1R^2$ and R^2 represents a phenyl, 3-chlorophenyl, 4-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 4-iodophenyl, 4-methylphenyl, 4-methoxyphenyl, 3-carboxylphenyl or 4-carboxylphenyl group, then R^1 is an optionally substituted alkyl group.

17. A process for the preparation of a compound of the general formula I according to claim 16 which comprises reacting a compound of the general formula II



(II)

in which Q represents a hydrogen atom or trimethylsilyl group, with a suitable halogenating agent to form a compound of the general formula I in which Y represents a halogen atom; and, if desired, reacting the compound of general formula I thus formed either with a Grignard reagent of the general formula YMgX where Y is an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclylalkyl group and X is a halogen atom to form a compound of general formula I in which Y represents an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclylalkyl group or with an

amine of the general formula HNR^1R^2 where R^1 and R^2 are as defined in claim 13 to form a compound of general formula I in which Y represents a group $-NR^1R^2$ where R^1 and R^2 are as defined above.

18. A process according to claim 17 in which a compound of the general formula I in which Y represents a bromine atom is generated in situ by reacting a compound of the general formula II in which Q represents a trimethylsilyl group with bromotrimethylsilane.

19. A process for the preparation of a compound of the general formula I according to claim 16 in which Y represents an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclylalkyl group which comprises reacting 9,10-anhydroartemisinin with a compound of the general formula Y-H, where Y is as defined above, in the presence of a suitable Lewis acid.

20. A process for the preparation of a compound of the general formula I as defined in claim 1 in which Y represents an optionally substituted aryl or C-linked heteroaryl group which comprises reacting 10-trichloroacetimidoyl-10-deoxoartemisinin with a compound of the general formula Y-H, where Y is defined above, in the presence of a suitable Lewis acid.

21. A process according to claim 18 in which the 10-trichloroacetimidoyl-10-deoxoartemisnin is generated in situ by reacting a compound of formula II as defined in claim 17 in which Q represents a hydrogen atom with trichloroacetonitrile in the presence of a suitable base.

22. A process for the preparation of a compound of the general formula I as defined in claim 1 in which Y represents an optionally substituted aryl or C-linked heteroaryl group which comprises reacting a 10-acyloxyartemisinin compound in which the acyloxy group is of formula A-(C=O)-O-, where A represents an optionally substituted alkyl, cycloalkyl, aryl, aralkyl, heterocyclic or polycyclic group, with a compound of the general formula Y-H, where Y is as defined above, in the presence of a Lewis acid.

23. A pharmaceutical composition which comprises a carrier and, as active ingredient, a compound of the general formula I according to claim 16.

24. A compound of the general formula I according to claim 16 for use in the treatment and/or prophylaxis of a disease caused by infection with a parasite of the genus Plasmodium.

25. Use of a compound of the general formula I according to Claim 16 for the manufacture of a medicament for the treatment and/or prophylaxis of a disease caused by infection with a parasite of the genus Plasmodium.

26. A method for treating a disease caused by infection with a parasite other than an organism of the genus Plasmodium which comprises administering to a host in need of such treatment a therapeutically effective amount of a compound of the general formula I as defined in claim 1.

27. A method for treating a disease caused by infection with a parasite of the genus Plasmodium which comprises administering to a host in need of such treatment a therapeutically effective amount of a compound of the general formula I according to claim 16.

09743827 .073401

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) **International Patent Classification** 7 :
C07D 493/18, A61K 31/335, 31/35 // (C07D 493/18, 241:00) (C07D 493/18, 307:00) (C07D 493/18, 209:00) (C07D 493/18, 265:00) (C07D 493/18, 221:00)

A1

(11) **International Publication Number:** **WO 00/04024**

(43) **International Publication Date:** 27 January 2000 (27.01.00)

(21) **International Application Number:** PCT/GB99/02267

(22) **International Filing Date:** 14 July 1999 (14.07.99)

(30) **Priority Data:**
98305596.3 14 July 1998 (14.07.98) EP

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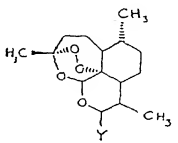
(81) **Designated States:** AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) **Title:** ANTIPARASITIC ARTEMISININ DERIVATIVES (ENDOPEROXIDES)

(57) **Abstract**

This invention relates to the use of certain C-10 substituted derivatives of artemisinin of general formula (I) in the treatment and/or prophylaxis of diseases caused by infection with a parasite, certain novel C-10 substituted derivatives of artemisinin, processes for their preparation and pharmaceutical compositions containing such C-10 substituted derivatives. The compounds are particularly effective in the treatment of malaria, neosporosis and coccidiosis.



(I)

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COMBINED DECLARATION AND POWER OF ATTORNEY	ATTORNEY DOCKET NO Le A 33 820

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name. I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought
on the invention entitled

ANTIPARASITIC ARTEMISININ DERIVATES (ENDOPEROXIDES)

the specification of which is attached hereto,

or was filed on **July 14, 1999**

as a PCT Application Serial No. **PCT/GB99/02267**

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s), the priority(ies) of which is/are to be claimed:

98305596.3	**Europe**	**July 14, 1998**
(Number)	(Country)	(Month/Day/Year Filed)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose the material information as defined in Title 37, Code of Federal Regulations, §1.56 which occured between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

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